Medical Library

End NOV 19 1943

THIS ISSUE CONTAINS ABSTRACTS

Vol. XLVIII NOVEMBER, 1943 No. 5

THE AMERICAN REVIEW OF TUBERCULOSIS

OFFICIAL JOURNAL
AMERICAN TRUDEAU SOCIETY

EDITOR
MAX PINNER, New York, N. Y.

EDITORIAL BOARD

JOHN ALEXANDER, Ann Arbor, Mich.
J. BURNS AMBERSON, JR., New York, N. Y.
E. R. BALDWIN, Saranac Lake, N. Y.
H. J. CORPER, Denver, Col.
F. S. DOLLEY, Los Angeles, Calif.
BRUCE H. DOUGLAS, Detroit, Mich.
L. U. GARDNER, Saranac Lake, N. Y.
ROSS GOLDEN, New York, N. Y.
ESMOND R. LONG, Philadelphia, Pa.
LEWIS J. MOORMAN, Oklahoma City, Okla.
D. W. RICHARDS, JR., New York, N. Y.

PUBLISHED MONTHLY
at Mount Royal and Guilford Avenues, Baltimore 2, Md.
by the
National Tuberculosis Association
Business Office, 1790 Broadway, New York 19, N. Y.

Copyright 1943, by the National Tuberculosis Association

CONTENTS

POTTENGER, F. M., AND POTTENGER, J. E. What is the Clinical and Epidemiological Significance of Rare Bacilli in Sputum 279

SASANO, K. T., AND MEDLAR, E. M. Egg-Yolk-Potato Medium. Its Efficiency for Demonstrating Small Numbers of Tubercle Bacilli 297

MEDLAR, E. M., ORDWAY, W. H., AND PESQUERA, G. S. Acid-Fast Bacilli in Patients of a Nontuberculous Medical Service 304

CUTLER, J. W. Standardization of Sedimentation Rate 314

DORMER, B. A., FRIEDLANDER, J., WILES, F. J., AND SCHAFFER, R. Tuberculin Patch Test. A Comparison with the Mantoux Intracutaneous Test 324

CORPER, H. J., AND COHN, MAURICE L. Immunization against Tuberculoprotein (Tuberculin) Anaphylaxis 329

RUDMAN, I. ELLIS. Pneumoperitoneum. Its Scope and Limitations in the Treatment of Pulmonary Tuberculosis 334

PIJOAN, M., AND SEDLACEK, B. Ascorbic Acid in Tuberculous Navajo Indians 342

Books 347

American Trudeau Society 356

Abstracts 69

BACK VOLUMES NOW AVAILABLE

A limited number of back issues of the AMERICAN REVIEW OF TUBERCULOSIS is available for immediate shipment to physicians and institutions wishing to fill gaps in their files, *on a volume basis only*, at a postpaid price of $4.00 per volume. Each volume contains six issues unless otherwise stated and the last issue of each volume contains a complete six-months cumulative index. All copies are in good condition.

Volumes 6, 7, 8, 9, 11, 12*, 13, 14, 16, 17, 18, 19, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 36, 37, 38, 39, 40, 44

THE FIRST FIVE VOLUMES ARE OUT OF PRINT

Containing as they do scientific reference data on all aspects of tuberculosis during a period of unremitting research and constant medical progress, these back volumes will make a particularly valuable addition to your library. The stock on hand is, in many cases, so extremely limited that this will probably be your last opportunity to obtain many of them.

A small quantity of single issues of the above volumes is also in stock and we will be glad to have your want list. The price is $1.00 per issue, postpaid.

* Volume 12 contains only four issues.

AMERICAN REVIEW OF TUBERCULOSIS, 1790 Broadway, New York 19, N.Y.

Entered as second-class matter March 9, 1917, at the post-office at Baltimore, Md., under the Act of August 24, 1912. Acceptance for mailing at special rate of postage provided for in section 1103, act of October 3, 1917. Authorized on July 2, 1918.

WHAT IS THE CLINICAL AND EPIDEMIOLOGICAL SIGNIFICANCE OF RARE BACILLI IN SPUTUM[1]

F. M. POTTENGER AND J. E. POTTENGER

When is so-called "converted sputum" converted? Our answer to this question is that converted sputum is not so completely and permanently converted as we have been thinking.

A review of the sputum examinations of hundreds of patients, undergoing treatment in the Pottenger Sanatorium and Clinic, and the follow-up examinations of a number of these for a period of years following discharge, indicates that completely and permanently negative sputum is rarely attained in those who have suffered from destructive and especially wide-spread pulmonary tuberculosis, even though they are clinically well and able to do their usual work. We have examined this question by submitting specimens of sputum from each patient in the Sanatorium to examination at regular intervals of from four to six weeks while under treatment, and from many patients at longer intervals after discharge—in some cases for nearly fifteen years.

TECHNIQUE

The technique for microscopical demonstration, using the dilution-flotation picric-acid method, and the technique for guinea pig inoculation have been previously discussed by one of us (1, 2, 3, 4, 5).

That this report may be properly understood it is necessary to state that these examinations were made according to carefully devised rules for collecting, preparing and examining specimens. No so-called samples and few direct smears were used in this report, nor has the Ziehl-Neelsen method of preparation of specimen been used except for comparison. The following rules have been followed:

(*1*) A sterilized bottle is provided and the patient is required to save everything expectorated, no matter where he thinks it comes from. The patient is not trusted to separate lung from throat sputum.

(*2*) Three-day specimens are routinely required and, if the first one is negative, four or five additional specimens are collected.

(*3*) The sputum is examined by the dilution-flotation picric-acid method and, when guinea pig inoculation is used, two-thirds of the homogenized specimen or its concentrate is injected. Inocula prepared for guinea pigs are subjected to two hours' contact at 37°C. with 0.5 per cent sodium hydrate. This is one-sixth to one-eighth the strength usually employed. The stronger solutions injure some strains of bacilli so that a negative result is obtained.

In the past few years both stained specimen and guinea pig must be negative before the patient is declared as even temporarily free from bacilli.

(*4*) Specimens are searched for a minimum of ten minutes (a total of about 200 microscopical fields) before they are declared negative.

[1] From The Pottenger Sanatorium and Clinic, Monrovia, California.

THE IMPORTANCE OF TECHNIQUE FROM A CLINICAL STANDPOINT

In order to understand the meaning of rare bacilli as described in our studies it is necessary to know the sensitivity of our technique. Corper estimated that in order to demonstrate bacilli by the usual Ziehl-Neelsen method there must be about 100,000 organisms present per cubic centimeter of substance to be examined. This has been confirmed by one of us (1). The dilution-flotation picric-acid method which we employ, when supported by accurate methods of collecting and preparing the specimen and a search of at least 200 microscopical fields (ten minutes' search) before declaring the specimen negative, shows an average superiority of about eighty-fold. Bacilli may be found when as few as 1,250 are present per cubic centimeter in heavy purulent sputum, and about 200 per cubic centimeter in thin watery material. We have used this method for twenty-six years, adding slight improvements with increased experience.

It does not seem to be sufficiently realized how inadequate and unsatisfactory the usual technique for examining sputum is; nor are the many factors which add to its inaccuracy appreciated. All methods used—whether they be those of staining, culture or guinea pig inoculation—have many inaccuracies connected with them. For example, guinea pigs have different degrees of susceptibility; and there are many things that interfere with the viability of the bacillus, such as the use of chemicals to destroy contaminating microörganisms. The medium used in cultures also is not the perfect ideal to secure growth. Then, too, different strains show variability in viability and tuberculogenic power.

Acceptance of the usual smear by the Ziehl-Neelsen method as sufficient for determining the presence or absence of tubercle bacilli in a given specimen is a cause of much inaccuracy both in diagnosis and estimating the results of treatment; for this may show grossly positive sputum as negative. When the Ziehl-Neelsen method of preparing specimens was first suggested it was such an advancement in diagnosis that it was immediately accepted and has continued to be used in the majority of laboratories regardless of the more accurate methods which have since been devised. Its comparative simplicity causes it still to be employed regardless of its inefficiency. It is only recently that clinicians and laboratory men have been impressed with the fact that a better method must be employed.

In our experience many patients are positive who have been pronounced bacillus-negative by good laboratories immediately before entering the sanatorium and only a small percentage of patients who have had positive sputum will stand the severe tests of having all sputum raised over a period of fifteen or thirty days examined without some bacilli being found. When the stage of rare bacilli, according to our technique, has been attained the numbers are small—often not more than one bacillus in 200 fields, sometimes even in 400 fields, but sufficient to show that the patient is not actually bacillus-free.

Just as this material was ready for publication a paper by Ordway, Medlar and Sasano (6) of the Metropolitan Life Insurance Company Sanatorium, Mount McGregor, New York, came to our notice. By using a sensitive technique their findings in patients while in the sanatorium are similar to our own. The statistics of our patients while in the sanatorium will be published in greater detail later. Since our experience goes back more than twenty years and includes not only patients while in the institution but others after returning to normal life, we are able to show that patients not only show a condition alternating between

rare bacilli and negative sputum while under treatment but that this same condition persists over succeeding years.

The following clinical histories and long-time record of sputum examinations of patients illustrate this fact.

CASE REPORTS

No. 10052, R. M.: Female, aged nineteen years. Entered Pottenger Sanatorium December 16, 1928. Observed fourteen and one-half years. Her mother suffered from advanced tuberculosis when patient was born. The patient was under my observation since birth. In October, 1928 she had an acute onset; temperature 102°F., accompanied by cough and sputum. Examination revealed infiltration above third rib with cavity, one inch in diameter, on the level of the first interspace in the right lung. Patient was treated in the sanatorium with the usual regimen plus tuberculin from December 16, 1928 to April 24, 1930. Since discharge from the sanatorium patient has lived a shielded, hygienic life but has been quite active, particularly in recent years. The first time bacilli were present in sufficient numbers to be found by the ordinary method of examination since leaving the sanatorium was on December 1, 1942, when one bacillus was found in every two fields. No reason for this was apparent in her clinical history, physical or X-ray examination. On April 8, 1943 the sputum had returned to the rare bacillus stage. This case well illustrates, on December 4, 1942, what we believe takes place regularly in tuberculous patients after they have become clinically well.

Sputum Record (No. 10052)

DATE	SPECIMEN	AMOUNT	BACILLI FOUND	DATE	SPECIMEN	AMOUNT	BACILLI FOUND
	days	*cc.*			*days*	*cc.*	
1928 Dec. 17	1	15	35 per field	1932 July 13	1	10	Neg. in 20 min.
1929 Jan. 29	1	25	40 per field	14	1	11	1 in 20 min.
Mar. 11	1	15	15 in 10 min.	15	1	10	Neg. in 20 min.
Apr. 24	1	30	4 in 10 min.	16	1	17	1 in 20 min.
June 5	1	20	1 in 10 min.	17	1	10	Neg. in 20 min.
July 15	1	15	2 in 10 min.	18	1	9	1 in 20 min.
Aug. 28	1	15	3 in 10 min.	19	1	10	Neg. in 20 min.
Oct. 9	3	15	3 in 10 min.	20	1	11	Neg. in 20 min.
Nov. 22	1	11	1 in 10 min.	21	1	9	Neg. in 20 min.
1930 Jan. 1	1	15	1 in 10 min.	22	1	10	Neg. in 20 min.
Feb. 9	3	65	Neg. in 15 min.	23	1	10	16 in 5 min.
Mar. 24	3	45	1 in 10 min.	24	1	10	4 in 10 min.
Oct. 13	3	35	Neg. in 10 min.	25	1	13	2 in 10 min.
19	3	35	Neg. in 10 min.	26	1	10	13 in 10 min.
Nov. 9	3	35	Neg. in 10 min.	27	1	8	Neg. in 20 min.
16	3	30	Neg. in 10 min.	28	1	11	Neg. in 20 min.
1931 Jan. 2	3	30	6 in 10 min.	29	1	11	Neg. in 20 min.
22	3	45	Neg. in 10 min.	Aug. 15	1	10	Neg. in 15 min.
July 19	3	30	Neg. in 15 min.	Sept. 26	2	10	Neg. in 10 min.
1932 Jan. 18	1	25	4 in 15 min.	Nov. 7	2	11	Neg. in 20 min.
Mar. 3	1	20	18 in 5 min.	1934 Jan. 6	2	15	Neg. in 10 min.
Apr. 14	3	45	1 in 10 min.	Mar. 27	1	8	Neg. in 10 min.
May 26	3	40	Neg. in 15 min.	Sept. 4	2	8	Neg. in 10 min.
July 6	1	10	Neg. in 10 min.	1936 Apr. 23	3	20	Neg. in 10 min.
9	1	9	Neg. in 20 min.	1938 Feb. 14	1	30	2 in 10 min.
10	1	12	Neg. in 20 min.	1939 June 21	2	20	7 in 5 min.
11	1	10	Neg. in 20 min.	Oct. 1	1	12	7 in 5 min.
12	1	11	Neg. in 20 min.	1942 Dec. 4	3	20	1 in 2 fields
				1943 Apr. 8	3	22	36 in 10 min.

No. 10698, C. W. B.: Male, aged thirty-five years. He was first examined January 21, 1929 and observed for fourteen years. He has extensive proliferative tuberculosis through left lung; mild in upper left. He was never a patient in the Pottenger Sanatorium, except for phrenic operation. He had been treated since August, 1926 at Tucson, Arizona. He was examined by us repeatedly from 1929 to 1943. In January, 1935 sputum showed several bacilli per field which continued until February, 1937. On account of this we advised a phrenic crush which was done October 22, 1936. Since then he has not had sufficient numbers of bacilli to be found on ordinary examination. During periods of increased bacilli patients are apt to have an endogenous reinfection. The chances of such occurring are especially great in case the patient is living under bad conditions and doing strenuous work, but not so great where the patient lives a hygienic life, as this patient did.

Sputum Record (No. 10698)

DATE	SPECIMEN	AMOUNT	BACILLI FOUND	DATE	SPECIMEN	AMOUNT	BACILLI FOUND
	days	*cc.*			*days*	*cc.*	
1929 Jan. 29	½	0.5	3 per field	1938 Mar. 25	1	6	Neg. in 10 min.
Nov. 3	1	2	6 in 10 min.	May 26	3	8	Neg. in 10 min.
1930 May 23	2	3	Neg. in 10 min.	July 27	2	2	4 in 5 min.
1933 Jan. 6	2	3	1 per field	Dec. 11	2	5	Neg. in 10 min.
1934 Mar. 3	3	3	11 in 5 min.	1939 Mar. 31	2	5	1 in 10 min.
June 2	2	3	23 in 5 min.	May 24	1	8	1 in 3 fields
Oct. 31	1	0.5	18 in 5 min.	Sept. 25	2	6	8 in 5 min.
1935 Jan. 22	2	2	1 in 5 fields	1940 Mar. 20	2	5	4 in 10 min.
Oct. 19	2	3	1 in 2 fields	1941 May 19	1	5	2 in 10 min.
1936 Mar. 18	1	0.7	7 per field	July 13	2	7	Neg. in 10 min.
Aug. 14	2	1.5	1 in 2 fields	Nov. 18	1	4	1 in 10 min.
Oct. 11	2	1	1 per field	1942 July 14	2	7	Neg. in 10 min.
1937 Feb. 26	1	1.5	14 in 5 min.	Nov. 10	2	7	3 in 10 min.
May 19	2	1	7 in 5 min.	1943 Mar. 6	2	7	4 in 10 min.
Aug. 19	2	1.5	10 in 5 min.				

No. 10257, H. S.: Male, aged twenty-four years. He was first examined September 14, 1931 and observed for eleven and one-half years. Patient had extensive bilateral tuberculosis of the fibrocaseous type with small areas of necrosis which finally healed with extensive calcification. The left lung was involved throughout, the right lung in the upper half. An ambulatory patient treated in clinic with open air, rest, general hygienic measures and tuberculin at different periods from April, 1933 to June, 1935. Since that time he finished his college course and has been teaching steadily until the present time. After one year of markedly positive sputum, bacilli became rare and absent and remained so except on September 20, 1936 when, without any known reason, his sputum showed one bacillus per field. Since then his sputum has continued to show rare bacilli and negative. During the past eight years he has been in excellent condition and has had no inconvenience. He carries on his work and lives a normal life.

Sputum Record (No. 10257)

DATE	SPECIMEN	AMOUNT	BACILLI FOUND	DATE	SPECIMEN	AMOUNT	BACILLI FOUND
	days	*cc.*			*days*	*cc.*	
1932 Jan. 29	2	3	10 per field	1934 Sept. 22	3	5	1 in 10 min.
May 27	1	10	2 per field	Nov. 13	3	13	1 in 10 min.
Aug. 25	3	15	30 per field	Dec. 19	2	7	2 in 10 min.
Dec. 7	3	8	12 in 10 min.	1935 Jan. 31	3	10	5 in 10 min.
1933 Apr. 1	3	5	2 in 10 min.	Mar. 18	3	12	2 in 10 min.
June 22	3	3	3 in 10 min.	May 27	3	30	Neg. in 10 min.
Sept. 18	3	3	Neg. in 15 min.	July 15	3	12	1 in 15 min.
Oct. 26	1	7	6 in 5 min.	Sept. 20	1	7	1 per field
Nov. 22	3	3	Neg. in 10 min.	Dec. 24	1	5	Neg. in 10 min.
1934 Jan. 4	3	6	Neg. in 10 min.	1937 June 7	2	12	21 in 5 min.
Mar. 16	3	5	Neg. in 10 min.	1939 Apr. 7	1	12	7 in 5 min.
June 30	3	6	2 in 10 min.				
Aug. 10	3	5	8 in 10 min.				

No. 10243, M. C.: Female, aged nineteen years. She entered Pottenger Sanatorium March 25, 1932 and was observed for eleven years. She took ill in 1929 with severe cold and cough which persisted. She rested about four months, after which she was up and down, part of the time in school. Cough continued. She had marked infiltration throughout entire right lung, largely proliferative with small cavities opposite second and fourth interspaces. She was in sanatorium eighteen months and was treated by usual physiologic methods and tuberculin. After leaving the sanatorium she finished her college course and has been living practically a normal life since. This patient has been studied more intently than any other that we have followed. From March 7, 1940 to June 24, 1942 her sputum was negative on every examination except the specimen of June 24, 1942. This is interesting because it occurred in the last of five consecutive three-day tests.

Sputum Record (No. 10243)

DATE	SPECIMEN	AMOUNT	BACILLI FOUND	DATE	SPECIMEN	AMOUNT	BACILLI FOUND
	days	*cc.*			*days*	*cc.*	
1932 Mar. 19	2	7	15 per field	1937 May 3	3	0.5	Neg. in 10 min.*
27	1	5	105 per field	6	3	1	Neg. in 10 min.*
May 10	3	4	15 per field	Nov. 25	3	0.7	Neg. in 10 min.†
June 19	3	1	90 in 10 min.	Dec. 6	6	1	Neg. in 10 min.†
Aug. 2	3	1.5	25 per field	12	3	0.3	Neg. in 10 min.†
Sept. 13	3	2	50 in 10 min.	14	3	0.3	Neg. in 10 min.†
Oct. 28	3	2	5 per field	1938 Apr. 6	9	0.5	1 per field†
Dec. 5	3	2.5	50 per field	11	6	0.5	Neg. in 10 min.
1933 Jan. 17	3	3	15 per field	Sept. 30	9	2	Neg. in 10 min.
Feb. 26	3	3	45 per field	Nov. 30	3	1	Neg. in 10 min.
Apr. 13	3	6	75 per field	Dec. 5	3	0.8	Neg. in 10 min.
May 25	3	7	20 in 10 min.	1939 Jan. 11	3	1.5	Neg. in 10 min.
July 4	3	10	16 in 10 min.	20	1	0.5	Neg. in 10 min.
Aug. 14	3	3	1 in 2 fields	June 23	3	0.5	Neg. in 10 min.
Nov. 17	3	2	7 in 10 min.	29	1	0.5	1 in 10 min.
1934 Feb. 20	3	0.5	2 per field	30	3	0.5	Neg. in 10 min.
May 10	3	3	Neg. in 10 min.	Oct. 17	3	0.6	Neg. in 10 min.
Aug. 24	3	1	Neg. in 10 min.	20	3	1	Neg. in 10 min.
Dec. 7	3	4	3 in 10 min.	26	3	2	1 in 10 min.
1935 Jan. 21	1	3	32 in 10 min.	28	3	1.5	Neg. in 10 min.
May 13	3	0.3	Neg. in 10 min.	Nov. 3	3	1.1	3 in 10 min.†
June 3	3	1.5	34 in 10 min.	1940 Feb. 27	3	6.8	90 in 10 min.
14	3	0.75	Neg. in 20 min.	Mar. 1	3	2	1 in 2 fields
21	3	0.05	Neg. in 20 min.	5	3	0.8	6 in 10 min.
26	3	1	Neg. in 10 min.	7	3	1.3	Neg. in 10 min.
July 5	3	0.5	Neg. in 20 min.	10	3	1.3	Neg. in 10 min.
Sept. 9	3	1.5	Neg. in 10 min.	Aug. 6	3	1.2	Neg. in 10 min.
Nov. 18	3	1	Neg. in 10 min.	9	3	1.3	Neg. in 10 min.
29	3	8	Neg. in 10 min.	12	3	0.4	Neg. in 10 min.
Dec. 3	3	1.5	Neg. in 10 min.*	15	3	0.6	Neg. in 10 min.
6	3	0.5	Neg. in 10 min.	18	3	0.2	Neg. in 10 min.
1936 May 13	3	0.2	Neg. in 10 min.	Apr. 3	6	1.2	Neg. in 10 min.*
15	3	1	Neg. in 10 min.	9	6	2.7	Neg. in 10 min.*
19	3	0.1	Neg. in 10 min.	12	3	1.8	Neg. in 10 min.*
Dec. 25	3	0.1	1 in 20 min.	1942 June 12	3	1.1	Neg. in 10 min.
1937 Jan. 4	3	1	Neg. in 10 min.	15	3	0.3	Neg. in 10 min.
Apr. 20	3	1	Neg. in 10 min.	18	3	1.4	Neg. in 10 min.
23	3	0.5	Neg. in 20 min.*	21	3	1.8	Neg. in 10 min.
26	3	0.1	Neg. in 10 min.*	24	3	0.3	1 in 10 min.
29	3	0.2	Neg. in 10 min.*				

* Guinea pig negative.
† Guinea pig positive.

No. 10338, E. S. D.: Female, aged twenty-two years. Entered the Pottenger Sanatorium June 5, 1933 and left September 24, 1933. She was observed ten years. Patient had been below par for two years. She had frequent colds which persisted, and gradually increasing malaise. In January, 1933 she began to cough and raised one ounce of sputum per day. Six months prior thereto she had acute pleurisy which was not considered serious. All symptoms were exaggerated following appendectomy in 1933. Sputum, examined June 1 for the first time, was found positive for tubercle bacilli. Examination June 5, 1933 showed extensive tuberculous infiltration through the upper lobe of right lung, much of which was of a soft exudative nature. In the second interspace was a cavity one inch in diameter. There was a slight involvement at the left apex. Patient was given the usual sanatorium treatment, plus tuberculin, with a rapid decline in numbers of bacilli. She refused both pneumothorax and phrenic. She was obliged to leave the sanatorium and continue rest treatment at home. One year later she still had one bacillus per field, after which the bacilli became rare and then the sputum negative. In 1936 bacilli again returned in fairly large numbers. On July 27, 1936 a temporary phrenic was done which did not close the cavity. The latter part of 1936 and through 1937 her sputum again showed numerous bacilli per field. In April, 1940 she reëntered the sanatorium. Pneumothorax was instituted April 17, 1940, which proved unsuccessful in closing the cavity. This was continued but a short time and the lung was allowed to expand, and in so doing closed the cavity. Her sputum entirely disappeared and she has had no sputum since June 23, 1940. This patient was not considered clinically well during 1935 and 1936, although her sputum was negative most of the time.

Sputum Record (No. 10338)

DATE	SPECIMEN	AMOUNT	BACILLI FOUND	DATE	SPECIMEN	AMOUNT	BACILLI FOUND
	days	*cc.*			*days*	*cc.*	
1933 June 6	1	8	30 per field	1936 Apr. 13	3	5	4 in 10 min.
July 21	3	1	3 per field	June 14	3	2	Neg. in 10 min.
Aug. 29	1	5	4 per field	Aug. 30	3	2	Neg. in 10 min.
1934 Mar. 20	2	5	1 per field	Nov. 26	1	1	10 per field
June 20	2	5	1 per field	1937 Feb. 23	3	3	1 in 2 fields
1935 Apr. 12	3	6	5 in 3 min.	July 9	2	6	15 per field
June 7	3	6	Neg. in 10 min.	Sept. 26	3	1	Neg. in 10 min.
Aug. 1	1	1	Neg. in 10 min.	1940 Apr. 14	1	2.5	30 per field
Sept. 18	3	5	Neg. in 10 min.	May 26	1	2	14 in 5 min.
Nov. 6	3	7	Neg. in 10 min.	June 23	1	0.5	10 per field
1936 Jan. 1	3	6	Neg. in 15 min.	Patient has had no sputum since.			
Feb. 16	3	3	3 in 5 min.				

No. 10416, M. K.: Female, aged twenty-eight years. Entered Pottenger Sanatorium March 24, 1934 and was observed nine years. Patient had an extensive bilateral tuberculosis, largely proliferative in character, with very little ulceration and small amount of sputum. She left the sanatorium July 9, 1934, after which she was examined at frequent intervals. On February 26, 1936 a small cavity was developing in the upper left lung. On May 18, 1937 there was increased activity. On October 20, 1937 the cavity was definitely excavated. She married in the spring of 1937, and was quite active, doing considerable walking and many little chores about the house. She was examined January 6, 1938 when she complained of having a cold accompanied by a sore throat and increased cough. It will be noted that at this time her sputum showed an increase in bacilli. She made a trip back to New Jersey, continued feeling tired and had increased cough and expectoration. She returned from her trip with her tuberculosis markedly reactivated and entered the sanatorium September 7, 1938, at which time her sputum showed 30 bacilli per field. The cavity in the upper portion of the left lung was far more distinct than it had been previously. On October 18, 1938 a left phrenicectomy was done. The cavity decreased in size and there was some clearing in the areas. On February 3, 1939 pneumoperitoneum was started. Patient left the sanatorium March 28, 1940, and the pneumoperitoneum was continued until March 13, 1941. It will be noted that her sputum became negative after the pneumoperitoneum and has remained so. This patient developed a complicating tuberculosis of the kidney which so far is mild and has produced no inconvenience. Bacilli were first found in the urine in November, 1939, and have continued to be present in small numbers. She was delivered of a baby by Caesarean section on January 9, 1943, and she continues in excellent condition. It will be noted that the increase in bacilli to 30 bacilli per field which attended the reactivation of her disease which began in January, 1938, dropped back to rare bacilli very quickly, but returned in one year, after which she again went into the negative and rare-bacilli stage and has remained so until now. The disease seems to be well healed. This case illustrated the danger of reactivation and endogenous reinfection which is always present until the lesion is healed.

Sputum Record (No. 10416)

DATE	SPECIMEN	AMOUNT	BACILLI FOUND	DATE	SPECIMEN	AMOUNT	BACILLI FOUND
	days	*cc.*			*days*	*cc.*	
1934 Mar. 26	1½	2.5	1 per field	1939 Sept. 19	3	7	Neg. in 10 min.
May 9	2	6	1 in 10 min.	Nov. 3	3	8	Neg. in 10 min.
June 13	2	10	Neg. in 10 min.	28	3	4.4	Neg. in 10 min.†
Oct. 12	1	10	11 in 5 min.	Dec. 1	3	6.8	Neg. in 10 min.
1935 Jan. 12	2	2.5	2 in 10 min.	4	3	5.3	Neg. in 10 min.†
June 20	2	7	Neg. in 10 min.	7	3	2	Neg. in 10 min.
1936 Oct. 11	3	2	Neg. in 10 min.	10	3	4.0	Neg. in 10 min.†
1937 Jan. 29	2	3	5 in 5 min.	13	3	5.1	Neg. in 10 min.
May 2	3	5	8 in 5 min.	1940 Jan. 23	3	2.4	Neg. in 10 min.
1938 Jan. 11	2	7	1 in 3 fields	Mar. 5	3	2	1 in 10 min.†
Sept. 10	3	15	30 per field	Nov. 18	3	1.6	9 in 5 min.
Oct. 16	3	5	20 in 5 min.	1941 Mar. 13	3	3.2	Neg. in 10 min.
Dec. 1	3	7	17 in 10 min.	July 24	3	1.6	Neg. in 10 min.
1939 Jan. 8	3	5	50 per field	Oct. 1	3	6	Neg. in 10 min.
Feb. 24	3	3	2 in 10 min.	1942 Jan. 19	3	3	Neg. in 10 min.
Apr. 2	3	2	Neg. in 10 min.	June 12	3	1.2	Neg. in 10 min.
May 16	3	3	Neg. in 10 min.	Sept. 14	5	5	Neg. in 10 min.
June 25	3	4	Neg. in 10 min.	20	5	5	Neg. in 10 min.*
				27	5	3.6	Neg. in 10 min.*
				Dec. 12	3	5	Neg. in 10 min.
				1943 Mar. 1	3	5	Neg. in 10 min.

* Guinea pig negative.
† Guinea pig positive.

No. 10538, P. H.: Male, aged fifty-seven. Entered Pottenger Sanatorium July 24, 1935 and was observed eight years. He had a moderate tuberculous infiltration to the second rib in both lungs, proliferative in type. Behind the first rib in the left lung was a small cavity. Patient also had bronchiectasis which was moderately severe. He gave a history of having first spat blood in 1908. He had always been subject to colds with bronchitis and considerable wheezing, but worked steadily until June 1, 1935, when positive sputum was found. On entering the sanatorium he had 65 cc. of sputum in one day with one bacillus in every two fields. On being put to bed with the usual sanatorium regimen, plus tuberculin, the sputum became negative and bacilli were not found again until May, 1936. From that time until this, he has been examined at infrequent intervals and his sputum has varied between rare bacilli and negative, but no reactivation of the disease has ever taken place, although it will be noted that on November 4, 1941 his sputum showed 20 bacilli per field. This was following an acute bronchitis.

Sputum Record (No. 10538)

DATE	SPECIMEN	AMOUNT	BACILLI FOUND	DATE	SPECIMEN	AMOUNT	BACILLI FOUND
	days	*cc.*			*days*	*cc.*	
1935 July 29	1	65	1 in 2 fields	1936 Sept. 15	1	30	Neg. in 10 min.
Sept. 5	1	30	Neg. in 10 min.	Oct. 29	1	30	Neg. in 10 min.
Oct. 13	2	70	Neg. in 10 min.	Dec. 7	1	35	Neg. in 10 min.
Nov. 28	2	65	Neg. in 10 min.	1937 Jan. 19	1	80	Neg. in 10 min.
1936 Jan. 8	2	60	Neg. in 10 min.	Mar. 1	2	75	Neg. in 10 min.
Feb. 17	2	50	Neg. in 10 min.	June 22	2	75	1 in 10 min.
Apr. 1	2	55	Neg. in 10 min.	Nov. 26	2	110	13 in 10 min.
May 12	2	60	Neg. in 10 min.	Dec. 28	3	140	Neg. in 10 min.
21	3	60	Neg. in 10 min.	1938 Mar. 16	1	50	1 in 10 min.
24	3	65	Neg. in 10 min.*	Sept. 7	2	95	5 in 10 min.
27	3	100	1 in 20 min.†	1939 Oct. 11	2	75	Neg. in 10 min.
30	3	95	3 in 60 min.†	1940 Aug. 7	1	55	4 in 10 min.
June 2	3	100	Neg. in 10 min.*	1941 Nov. 4	½	35	20 per field
17	3	130	Neg. in 10 min.	1943 Feb. 10	½	40	Neg. in 10 min.
25	1	4	Neg. in 10 min.				
Aug. 4	1	40	Neg. in 10 min.				

* Guinea pig negative.
† Guinea pig positive.

No. 10707, R. L. P.: Male, aged thirty years. He was observed seven years. He entered Pottenger Sanatorium November 19, 1936, suffering from tuberculous infiltration in the upper lobe of the right lung. This was a recent invasion engrafted on an old proliferative lesion. There was also some fibrous infiltration in the lower lobe of the right lung. Extending out in the left lung from the hilum was a mild infiltration. Patient remained in the sanatorium eleven months. This patient never showed many bacilli. The diagnosis could not have been made by an ordinary smear; but the fact of rare bacilli and negative sputum did not indicate that the patient was healed. During the time of treatment the infiltration in the lung absorbed, leaving the lung area almost entirely clear. This patient was studied intently.

Sputum Record (No. 10707)

DATE	SPECIMEN	AMOUNT	BACILLI FOUND	DATE	SPECIMEN	AMOUNT	BACILLI FOUND
	days	*cc.*			*days*	*cc.*	
1936 Nov. 22	3	17	2 in 10 min.	1937 May 28	1	11	Neg. in 10 min.
26	3	20	1 in 10 min.	29	1	13	Neg. in 10 min.
29	3	15	Neg. in 10 min.	30	1	13	Neg. in 10 min.
Dec. 2	3	20	Neg. in 10 min.	June 1	1	15	Neg. in 10 min.
5	3	20	Neg. in 10 min.	2	1	15	Neg. in 10 min.*
14	3	10	Neg. in 10 min.†	3	1	9	Neg. in 10 min.*
18	2	20	Neg. in 20 min.	4	1	13	Neg. in 10 min.*
20	2	10	Neg. in 10 min.	5	1	12	Neg. in 10 min.*
22	2	10	1 in 10 min.	6	1	14	Neg. in 10 min.*
24	2	12	Neg. in 10 min.	7	1	10	Neg. in 10 min.*
26	2	10	Neg. in 10 min.	8	1	10	Neg. in 10 min.†
1937 Feb. 9	3	25	1 in 10 min.	17	3	25	Neg. in 10 min.
Mar. 23	3	18	Neg. in 10 min.	July 28	3	20	Neg. in 10 min.
May 6	3	35	Neg. in 10 min.	Sept. 6	3	20	Neg. in 10 min.
22	1	14	Neg. in 10 min.*	1938 Sept. 12	2	10	Neg. in 10 min.
23	1	11	Neg. in 10 min.*	Dec. 9	1	7	Neg. in 10 min.
24	1	13	Neg. in 10 min.*	1940 May 2	2	6.6	Neg. in 10 min.
25	1	20	Neg. in 10 min.*	Sept. 9	2	6	Neg. in 10 min.
26	1	13	Neg. in 10 min.†	1941 Oct. 25	3	12	Neg. in 10 min.
27	1	11	Neg. in 10 min.†	1942 Sept. 29	2	7	Neg. in 10 min.

* Guinea pig negative.
† Guinea pig positive.

No. 10739, W. A.: Male, aged twenty-four years. He was observed six years. He entered Pottenger Sanatorium March 2, 1937. Early tuberculosis was discovered in 1928. He was permitted to continue going to school but taking extra rest outside of school hours. In 1930 cough returned for several months. In 1932 he started work. He had some pleurisy. In 1933 X-ray film was taken and a cavity was found in right lung. Patient was treated at home. In March 1937 activity was found in both lungs with a cavity one inch in diameter opposite the second rib on the left side for which he entered Pottenger Sanatorium. He was put on the usual regimen with bath privileges only, and treated with shotbag over left apex and tuberculin. It will be noted that his bacilli decreased rapidly from 75 per field to rare and continued until October 9, 1938, when 3 bacilli per field were found. There was no evidence of any increased activity shown by clinical symptoms or found on physical or X-ray examination. His sputum again returned to rare bacilli and has continued alternating between rare bacilli and negative until the present time. When the patient left the sanatorium May 20, 1940 he was sitting up eleven hours a day and walking four miles with ease. He immediately started work two hours a day, gradually increasing this and in a short time was doing a full day's work with ease.

Sputum Record (No. 10739)

DATE	SPECIMEN	AMOUNT	BACILLI FOUND	DATE	SPECIMEN	AMOUNT	BACILLI FOUND
	days	*cc.*			*days*	*cc.*	
1937 Mar. 5	2½	35	75 per field	1939 Dec. 7	3	40	1 in 3 fields
Apr. 11	1	30	2 in 10 min.	1940 Jan. 16	3	40	1 in 10 min.†
May 27	3	55	7 in 10 min.	Feb. 29	3	50	5 in 5 min.
July 5	3	30	Neg. in 10 min.	Apr. 9	3	45	Neg. in 10 min.
Aug. 19	3	25	Neg. in 10 min.	July 2	3	25	Neg. in 10 min.
Sept. 27	3	40	3 in 5 min.	Sept. 4	3	45	Neg. in 10 min.
Nov. 8	3	20	3 in 10 min.	Oct. 15	3	20	Neg. in 10 min.
Dec. 19	3	20	Neg. in 10 min.	Dec. 3	3	35	Neg. in 10 min.
1938 Jan. 30	3	15	Neg. in 10 min.	1941 Jan. 26	3	35	5 in 10 min.
Mar. 19	3	15	3 in 20 min.	Apr. 22	3	30	3 in 15 min.
22	3	12	Neg. in 10 min.*	June 2	3	50	1 in 10 min.
25	3	15	Neg. in 10 min.‖	Aug. 30	3	35	Neg. in 10 min.
28	3	18	5 in 5 min.†	Nov. 28	3	12	Neg. in 10 min.
Apr. 24	3	20	9 in 10 min.	1942 Feb. 24	3	10	Neg. in 10 min.
June 5	3	10	3 in 10 min.	June 6	3	15	Neg. in 10 min.
July 17	3	15	14 in 3 min.	Oct. 1	3	10	Neg. in 10 min.
Aug. 28	3	45	Neg. in 10 min.	1943 Feb. 25	3	8	Neg. in 10 min.
Oct. 9	3	50	3 per field	May 24	3	8	1 in 10 min.
Nov. 22	3	35	5 in 5 min.				
1939 Jan. 6	3	10	21 in 5 min.				
Feb. 14	3	25	1 in 10 min.				
May 9	3	20	Neg. in 10 min.				
June 18	3	20	1 in 10 min.				
Aug. 4	3	40	5 in 5 min.				
Sept. 12	3	25	7 in 5 min.				
Oct. 25	3	30	Neg. in 10 min.				

* Guinea pig negative.
† Guinea pig positive.
‖ 3 bacilli were found in 60 min. search.

No. 10737, S. B.: Female, aged twenty-eight years. She entered Pottenger Sanatorium February 25, 1937 and was observed six years. Physical examination showed tuberculous infiltration in the upper lobe of the right lung, mostly of an exudative type. A three-quarter-inch cavity was present opposite the first rib. Patient remained in the sanatorium eight months. This patient made a satisfactory recovery in a minimum of time. She was treated by rest in bed, shotbag over right lung, with the usual hygienic measures plus tuberculin. She left the sanatorium in eight months and continued following advice on the outside, returning for frequent examinations. She was delivered of a baby December 13, 1941. This case illustrates that it may be possible to become continuously bacillus-free, for we have found no bacilli now for six years.

Sputum Record (No. 10737)

DATE	SPECIMEN	AMOUNT	BACILLI FOUND	DATE	SPECIMEN	AMOUNT	BACILLI FOUND
	days	*cc.*			*days*	*cc.*	
1937 Feb. 28	3	10	15 per field	1937 Dec. 29	3	4	Neg. in 10 min.
May 20	3	10	1 in 3 fields	1938 Apr. 15	3	5	Neg. in 10 min.
June 27	3	20	10 per field				
Aug. 12	3	10	6 in 10 min.	At this time her sputum disappeared and she was not able to supply us with a sample until March 11, 1942, when she had 8 cc. in three days, which was negative.			
Sept. 20	3	8	Neg. in 10 min.				

No. 10802, W. B.: Male, aged seventeen years. He entered Pottenger Sanatorium September 21, and was observed six years. He gave a history of having symptoms resembling a cold in March, 1937, with pains in chest, cough and expectoration. Diagnosis of bronchitis was made. In July, 1937, the diagnosis of tuberculosis was made. On entering the sanatorium physical examination showed marked involvement from apex to third rib in both lungs. In the right first interspace was a cavity one inch in diameter, and in the second interspace another cavity slightly smaller. Patient was suffering from acute exudative tuberculosis. He was put to bed with shotbag over the right apex and allowed bathroom privileges only. He was given the usual sanatorium treatment and tuberculin. The sputum of this patient rapidly became negative. He was obliged to leave the sanatorium at the end of nine months. When he was up three hours and walking 3000 feet a day, he continued his program at home returning for examination and guidance at intervals of six or eight weeks. This case illustrates the rapidity with which acute cavities will heal under physiological methods alone. His sputum was quickly changed to negative.

Sputum Record (No. 10802)

DATE	SPECIMEN	AMOUNT	BACILLI FOUND	DATE	SPECIMEN	AMOUNT	BACILLI FOUND
	days	*cc.*			*days*	*cc.*	
1937 Sept. 24	3	18	75 per field	1937 July 7	3	4	Neg. in 10 min.*
Oct. 31	1	10	15 in 10 min.	10	3	3	Neg. in 10 min.*
Dec. 14	1	10	6 in 5 min.	14	3	5	Neg. in 10 min.*
1938 Jan. 23	2	20	2 per field	17	3	3	Neg. in 10 min.
Mar. 4	3	15	Neg. in 10 min.	Sept. 12	2	5	Neg. in 10 min.
Apr. 18	3	15	Neg. in 10 min.	Oct. 10	3	5	Neg. in 10 min.
May 30	3	10	Neg. in 10 min.	1939 Jan. 17	3	3	Neg. in 10 min.
June 2	3	8	Neg. in 10 min.	May 26	3	4	Neg. in 10 min.
5	3	5	Neg. in 10 min.	Oct. 9	3	4	Neg. in 10 min.
8	3	3	Neg. in 10 min.	1940 Sept. 6	3	3.6	9 in 5 min.
11	3	4	Neg. in 10 min.	1941 May 1	3	5	Neg. in 10 min.
14	3	5	Neg. in 10 min.	1942 Apr. 21	4	3.6	3 in 5 min.
17	3	5	Neg. in 10 min.				
July 3	3	4	Neg. in 10 min.*				

* Guinea pig negative.

DISCUSSION

In our experience in the acute predominantly exudative type of tuberculosis with soft-walled cavities and tissues which will readily compensate, as illustrated by cases Nos. 10737 and 10802, the stage of rare bacilli is usually quickly reached, often in a few weeks after the patient is put on treatment. This stage is usually attained whether we depend upon physiological measures alone or add some form of compression; although it may be attained a little sooner if a suitable collapse is obtained by pneumothorax. On the other hand, in the fibrocaseous types of the disease, large numbers of bacilli are often discharged from cavity walls for long periods of time. This is illustrated by case No. 10253, in whose sputum numerous bacilli persisted for a year. If the disease is otherwise healing in a satisfactory manner, this is of little significance when the patient is isolated and properly controlled in a sanatorium, but of greater importance if living in the home with other people. In case No. 10707, bacilli would never have been found by the Ziehl-Neelsen method.

Seven of the patients herein reported were treated in the institution during the active course of their disease and until discharged as clinically healed. Two were treated for only a short time in the institution; one was an in-patient only a few days for a phrenic operation, and one was treated as an out-patient in the clinic.

Since the sputum examinations reported in this paper show that patients are bacillus-carriers long after they are clinically well and able to assume their places in society as producers, certain practical questions arise: When can we disregard the presence of rare bacilli from the standpoint of safety to the patient and safety to those who associate with him? When can a patient be safely discharged as clinically well?

Our experience should be of value in answering these queries. So far not a single individual—adult or child—who has intimately associated with these patients has broken down with active tuberculosis, yet we cannot say with definiteness that no one has been infected; but if infection has occurred, the lesion has been of nonprogressive type. The apparent safety depends upon the fact that so few bacilli are discharged, and the care exercised by the patient who is warned always to destroy every particle of sputum.

There is probably greater danger to the patient, himself, in the rare bacillus stage than to those who associate with him. While only a few bacilli are discharged there may be many in the tissues and, after infection has taken place, the opportunity for endogenous spread is always present should conditions which disturb the architecture of the tubercles arise. However, our experience has been most fortunate. In the past twenty years we have had a minimum of patients who have had recurrences of clinical tuberculosis after being discharged as clinically well in spite of the presence of rare bacilli.

Every now and then irritating forces of various kinds may act upon quiescent foci which are apparently producing no damaging effect upon the patient and cause the discharge of bacilli in numbers larger than usual. This may be produced by any force which causes marked stimulation, such as an acute respiratory infection, meteorological changes and many subtle forces which are not so

evident. The fact that as soon as the acuteness of the episode is over the lesion usually assumes its former state of stability probably indicates that the organisms were discharged from a surface which, while open to the air passages, previously had not been giving off bacilli into the bronchial lumen, or had been discharging them in small numbers.

We are not inclined to look upon these occurrences as serious if they are of a temporary nature and the patient is properly directed at the time. Very different, however, is the case when an active lesion is still present, or when the increase in bacilli persists, or especially if the patient does not give proper heed to the occurrence. So far none of the patients in this group whom we had discharged as clinically well has had to be subjected to further treatment because of an increased number of bacilli temporarily appearing in the sputum. However, the 3 patients who had not been brought to a state of clinical healing all had recurrences of activity (cases Nos. 10338, 10416, and 10698).

Patients are often a great danger to themselves after the period of negative sputum has been attained because of being too willing to accept the fact of two or three negative reports as meaning that the lesion is healed and feeling that they are then able to guide themselves.

The danger of unhealed lesions is illustrated by cases Nos. 10338 and 10416, both of whom developed quite active disease after they had shown rare bacilli on repeated examinations. In case No. 10338 the sputum would have been negative by the Ziehl-Neelsen method at all times between and including April 12, 1935 and August 30, 1936, and in case No. 10416 from May 9, 1934 to May 2, 1937; yet neither of these patients were healed. These cases illustrate what so often follows insufficient treatment.

Our experience shows that the classification of healing must not depend upon a few negative examinations of sputum. The patient must from every angle give indications of a healed lesion. Contrast these 2 cases with cases Nos. 10052, 10243 and 10739, which had alternating negative and rare bacilli but who were not discharged until they were clinically arrested as determined by all available evidence. Their after-course has been satisfactory.

These exacting, long time studies throw light on some of the most serious problems presented in the diagnosis and treatment of tuberculosis. While we do not expect every laboratory to adopt such a technique and repeat such studies, yet we hope that the information which we have gained is of sufficient importance to cause at least a few enthusiasts to repeat them. In several instances, specimens were subjected to long periods of search—twenty minutes, forty minutes, an hour. It was the purpose to find out how nearly and how often patients become entirely bacillus-free. The fact that guinea pig inoculation was used in many instances adds additional accuracy to the report.

Obviously negative sputum is a term which differs widely in its meaning according to the conditions of examination. Since we rarely secure a continuously permanently negative sputum in chronic destructive lesions we do not use the absence of bacilli as a basis for discharging patients. We discharge them when rare bacilli are still found if we think they are clinically well and have reached

a stage of physical strength equivalent to that which will be necessary for carrying on their usual work. We try not to discharge any patient so long as there is doubt in our minds as to his condition and we feel fairly confident that he may secure a healing. We want to feel that he will remain well; otherwise treatment has failed.

As a test of strength we assume that a patient who is able continuously to walk from two to five miles with ease day after day (but still resting ten or twelve hours in bed) is physically fit. We have many conscientious patients doing eight hours' work and still resting ten hours in bed each day. While we would like to have all patients free from bacilli before discharge, we do not expect them to be so.

Many patients showing rare bacilli are able to begin doing two or three hours' work a day, which may be increased gradually until they do full eight hours. The partial guarantee of their safety in beginning work is the fact that they have stood up under this trial program of exercise and remained well while doing so. They are physically rehabilitated when their active treatment is finished.

Our patients are apprized of the fact that the numbers of bacilli discharged may increase with acute respiratory diseases, and they are told that it is necessary for them always to destroy every bit of sputum raised at such times and, furthermore, give themselves special care. It is surprising how relatively few acute respiratory infections patients have when they are isolated and follow hygienic rules, such as are enforced in the sanatorium, and how much milder attacks are after discharge, provided they continue to follow the same rules.

Our experience differs from that reported by Whitney and Dempsey (7) in which they state: "Patients with positive sputum at time of discharge have relatively little chance of survival; only one out of four thus handicapped was living at end of five years, whereas among those with no sputum or with negative sputum on discharge two out of three survived the five-year period." This undoubtedly means "positive" with one of the less sensitive methods. Many of our patients show rare bacilli in their sputum at the time of discharge from the sanatorium. Regardless of this fact, however, they are able to carry on their life's work and rarely show relapse.

This difference may be explained partly by the fact that, using a more sensitive method of examining sputum, our patients are probably farther advanced in healing when discharged, and partly by the higher economic status of our patients, for many of the sanatoria mentioned in this report are public institutions.

It will be remembered that the death rate from tuberculosis of the lower economic group is much greater than in the independent economic groups. The more unfavorable the environment in which patients must live and the lower the nutritive value of their food, the more necessary it is to prolong their treatment and then shield them afterwards; also the more necessary it is to rehabilitate them before leaving the shelter of the institution. Instead, this group is usually discharged earlier than those of a better social and economic status and are returned to their homes without having been rehabilitated and are then given a

minimum of after-care. Two of the greatest faults in our present method of treating tuberculosis is that we are trying to cure tuberculosis faster than healing can take place, and are failing to provide patients with conditions which will enable them to continue healing after they have been returned to their homes. The result of this practice is too often a reactivation after discharge.

The histories of our cases show that negative sputum even by this exacting technique does not indicate that the patient is healed and ready for discharge. They also show that we must in other respects change our ideas of the meaning of rare bacilli in relation to tuberculosis. On the other hand, every patient who has an infection of the lung with rare bacilli in his sputum is not necessarily suffering from active disease, nor is he necessarily a menace to those who live with him. The presence of rare bacilli by this exacting technique shows that tuberculosis is or has been present in a clinical form without determining the state of activity at the time. In this it is not unlike the tuberculin test which indicates infection only.

Our findings throw the diagnosis of active tuberculosis back upon the clinician and require that he depend upon his clinical sense for his opinion. It is only after the careful analysis of all data that we can determine the condition of the patient. The X-ray examination does not give a complete answer to activity or arrestment; the tuberculin test does not give us definite information; nor does the presence of rare bacilli, when a sensitive technique is employed, differentiate between clinically active and inactive disease. So this bit of increased information regarding rare bacilli, like the X-ray film and the tuberculin test, may for the time being throw more uncertainty into an already confused field. It emphasizes that diagnosis must depend upon a well cultivated clinical sense.

When the meaning of rare bacilli is fully understood it should add to the intelligent approach to the solution of the ever more difficult problems which surround tuberculosis in its waning period. (*1*) It teaches the necessity for the adoption of a more sensitive technique for examining sputum and the acquiring of a well trained clinical sense by which the status of the patient may be estimated. (*2*) It especially teaches the necessity of adequate treatment in order to overcome the tendency to relapse. (*3*) When we have accomplished the best that we can accomplish, a few bacilli may still persist in the sputum, but the small numbers present are probably of little significance from the community standpoint. Such patients may expel less than one thousand bacilli in twenty-four hours, and those only occasionally. It would be extremely rare for those bacilli to be brought into sufficiently close contact with associates to cause infection.

SUMMARY

1. Tuberculous patients who have been studied over periods of time varying from six to fourteen and a half years are cited to show that rare bacilli may persist in the sputum over long periods of time.

2. Our experience indicates that, if the patient is clinically well, there is little

danger from rare bacilli found by very sensitive methods, either to himself or to those with whom he associates.

3. Sometimes larger numbers of bacilli will be temporarily discharged by one who has been clinically well and carrying on his regular work without hindrance, the patient returning at once to the rare or negative stage, without reactivation of his disease taking place.

4. The persistence of bacilli occurs whether the patient has been treated by physiological methods alone or by collapse procedures. In our experience no method will regularly produce a continuously negative sputum.

5. The presence of rare bacilli in sputum does not necessarily mean that the patient is suffering from clinically active tuberculosis. On the other hand, it shows that active tuberculosis has been present. This finding may be consistent with good health and full working capacity.

6. Patients with rare bacilli are probably of greater danger to themselves than to those with whom they associate, because bacilli are present in the tissues and may produce endogenous spread in case the proper stimulus is present. As regards the danger to others the number of bacilli expectorated is so small—in many of our cases not being more than a few hundred on some days and negative on many others—that, unless conditions are especially propitious for infection, a sufficient number of bacilli to cause implantation would probably not gain entrance to the tissues of those with whom the patient associates. The danger, however, would probably be greater to children than to adults, and to the less resistant than to the stronger.

7. In its bearing upon the problem of clinical tuberculosis, the presence of rare bacilli in the sputum, as determined by exacting techniques, is in much the same category in its relationship to diagnosis and cure as the tuberculin test. Of itself it only gives evidence of limited value. The true estimate of the case must depend upon highly trained clinical judgment.

SUMARIO

1. Cítanse tuberculosos estudiados por períodos de tiempo que variaron de seis a catorce años y medio para demostrar que puede persistir alguno que otro bacilo en el esputo durante períodos prolongados.

2. La experiencia del A. indica que si el enfermo está clínicamente bien encierran poco peligro los raros bacilos descubiertos con técnicas muy delicadas, ya para aquel mismo o para sus allegados.

3. A veces puede expulsar temporalmente grandes cantidades de bacilos un individuo que ha estado clínicamente bien y ejecuta sin dificultad sus tareas regulares, volviendo el sujeto en el acto al período de negatividad o de rareza de bacilos sin que se reactive la dolencia.

4. La persistencia de los bacilos tiene lugar, ya haya sido tratado el enfermo exclusivamente con técnicas fisiológicas, o con procedimientos de colapso, sin que ningún método produzca con regularidad un esputo constantemente negativo.

5. La presencia de raros bacilos en el esputo no denota forzosamente que el individuo padezca de tuberculosis clínicamente activa, pero sí denota que ha

existido tuberculosis activa, lo cual puede ser compatible con un estado de buena salud y plena capacidad para el trabajo.

6. Los enfermos con raros bacilos son probablemente más peligrosos para sí propios que para sus convivientes, pues los bacilos presentes en los tejidos pueden provocar propagación endógena, de existir un estímulo adecuado. En cuanto al peligro para los demás es tan pequeño el número de bacilos expectorados —en muchos de los casos del A. no pasaban de algunos centenares en algunos días, y en otros muchos días no había ninguno—que a menos que las condiciones se presten por demás para la infección, probablemente no penetrará en los tejidos de aquéllos con quienes se asocia el enfermo un número suficiente de bacilos para lograr implante. Sin embargo, el peligro sería probablemente mayor para los niños que para los adultos, y mayor para los menos resistentes que para los fuertes.

7. En lo que toca al problema de la tuberculosis clínica, la presencia de escasos bacilos descubiertos en el esputo con una técnica minuciosa, se encuentra en su relación con el diagnóstico y curación más o menos en la misma categoría que la reacción a la tuberculina, pues por sí misma sólo aporta datos de valor limitado. La verdadera justipreciación del caso tiene que fundarse en el criterio clínico avezado.

REFERENCES

(1) Pottenger, Joseph E.: The demonstration of rare tubercle bacilli in sputum, Am. Rev. Tuberc., 1931, *24*, 586.
(2) Pottenger, Joseph E.: Technique of sputum examination, Ibid., 1939, *40*, 581.
(3) Pottenger, Joseph E.: Controlled staining of Mycobacterium tuberculosis, Ibid., 1942, *45*, 549.
(4) Pottenger, Joseph E.: Counterstains in demonstrating Mycobacterium tuberculosis in sputum, Ibid., 1942, *45*, 558.
(5) Pottenger, Joseph E.: Present practice in staining Mycobacterium tuberculosis in representative institutions, Ibid., 1942, *45*, 568.
(6) Ordway, W. H., Medlar, E. M., and Sasano, K. T.: Routine application of concentration, culture, and guinea pig inoculation for the demonstration of tubercle bacilli in tuberculous cases under treatment, Yale J. Biol. & Med., 1943, *15*, 353.
(7) Whitney, Jessamine S., and Dempsey, Mary V.: A study of patients discharged alive from tuberculosis sanatoria in 1933. National Tuberculosis Association, Social Research Series, No. 8.

EGG - YOLK - POTATO MEDIUM[1]

Its Efficiency for Demonstrating Small Numbers of Tubercle Bacilli

K. T. SASANO AND E. M. MEDLAR

Since the discovery and successful cultivation, on artificial medium, of the tubercle bacillus by Koch (1882) the studies of acid-fast bacilli have gone through three major phases. The first phase dealt primarily with the procurement of a variety of strains from human, animal and other sources to determine the cultural and pathogenic properties of bacteria of this type. From the outset, studies revealed that cultivation of organisms of the acid-fast variety on artificial culture media was no easy task. This problem received the attention of Griffith and Griffith (1) who investigated a considerable variety of culture media. They found that the most useful medium for isolation of tubercle bacilli directly from tuberculous tissue was one of whole hen's egg or of egg-yolk. On such a medium they succeeded in obtaining primary cultures in 90 per cent of their attempts. They were the first, apparently, to determine that egg-white *per se* did not provide a suitable medium. They agreed with the observation of previous investigators that the addition of small amounts of glycerol to a medium enhances the growth of the human type of tubercle bacillus.

The primary interest of the second phase of study was in the production of tuberculin. Here the problem was to obtain a large amount of growth on liquid media. It was found that some persons gave a "false positive" tuberculin reaction because they were "allergic" to components of the broth employed in the liquid medium. The synthetic medium devised by Long (2) has proved to be a great aid is the solution of this problem. This medium yields abundant growth of bacilli once a strain becomes adjusted to the new environment.

The third and present phase is concerned primarily with the utilization of solid culture media to demonstrate tubercle bacilli in instances where these organisms are too few to be easily found in concentrates of sputa, pleural fluid, etc. In other words, the employment of the cultural method is now a useful routine diagnostic procedure. Because the bacilli are sparse in specimens where demonstration by culture is attempted it is necessary to concentrate the specimens to a minimum of sediment. This is attained by digestion with acid or alkali and subsequent centrifugation. Secondary bacteria often far outnumber the acid-fast bacilli and, unless they are held in check, will overgrow the slow-growing acid-fast bacilli. The control of the secondary organisms is obtained in part by the acid or alkali used in the digestion process. A further inhibition of growth of the organisms, surviving the acid or alkali treatment, is the incorporation of small amounts of such dyes as gentian violet, crystal violet, malachite

[1] From the Hegeman Memorial Laboratory, Metropolitan Life Insurance Company Sanatorium, Mount McGregor, New York.

green, etc., in the medium. Petroff (3), Petragnani (4) and Corper (5), among others, have been pioneer investigators in this field.

Many media have been devised in the search for one suitable for use in a routine diagnostic service and they usually have borne the name of their originators, for example, Dorset (1912), Petroff (1915), Löwenstein (1924), Petragnani (1926), Corper (1927), etc. In most instances hens' eggs have been the principal ingredient of these media. The one exception of note was the potato medium devised by Corper and Uyei (6). Other substances such as broth, milk, cream, potato, glycerine, etc., have been added to the egg in varying proportions and combinations. In each instance the type of medium reported has apparently yielded better results in the hands of the reporter than any other medium he had experimented with. In most studies the usefulness of a medium has been determined from studies of stock laboratory cultures. To claim that a medium, superior for cultivation of strains already accustomed to an artificial environment, will be equally efficient in stimulating the growth of a few bacilli present in a concentrate is hardly justifiable unless a suitable yardstick for comparison has been used.

METHODS AND RESULTS

In our studies of the efficiency of a medium for demonstrating few bacilli in concentrates we have utilized the results of guinea pig inoculation as the criterion for efficiency. This, admittedly, has been an expensive procedure but in search for a means of comparison none other was available. Throughout our studies concentrates have been divided into two approximately equal portions, one portion being used for the culture and the other for guinea pig inoculation.

For a number of years an egg-potato medium had been used in our routine diagnostic service concomitant with guinea pig inoculation. This medium yielded excellent results, equalling the guinea pig test where bacilli could be demonstrated in smears of concentrates. It failed to equal the results of guinea pig tests where smears of concentrates were negative. A search was begun for a more efficient medium. Among the media investigated was a group with varying amounts of egg-yolk in glycerine-agar. None of the combinations in this group equalled the efficiency of the egg-potato medium already in use. This experience suggested that in some way the agar base interferred with the growth of the bacilli, for a plain egg-yolk medium was a distinctly superior medium. On the chance that egg-white had an effect similar to agar, the composition of our egg-potato medium was changed so that the bulk of egg-white was eliminated and the proportion of egg-yolk increased. This medium proved to be superior to the routine medium in that a greater volume of growth was noted. At this time we were not cognizant of the excellent work that had been done by Griffith and Griffith. The egg-yolk-potato mixture was then substituted for the egg-potato medium in the routine service. This procedure was followed in order that the concentrates need not be divided into smaller portions. The composition and preparation of the egg-yolk-potato medium is as follows:

Stock Medium

Irish potato—peeled and finely ground	200 g.
Glycerol	60 cc.
Citric acid	0.2 g.
Blood powder	5 g.
Distilled water	1000 cc.

These ingredients are mixed and autoclaved for thirty minutes at 15 pounds' pressure. The mixture is then filtered through a double thickness of gauze to remove the coarsest particles of potato. Five-hundred cc. portions are put in flasks and are again autoclaved as before. This stock keeps well and may be stored for use as needed. The blood powder is obtained from guinea pig blood clots derived from animals which are sacrificed in our diagnostic service. The blood clot is thoroughly dried in an electrically heated oven at 60° C. After dehydration the clot is ground to a fine powder and stored for use as needed. Blood powder is used because it seems to add slightly to the efficiency of the medium.

Egg-yolk: Fresh hens' eggs are carefully cleaned with wet gauze. They are then placed in 80 per cent alcohol for two hours. The alcohol is decanted and the eggs are dried by brief and careful flaming. The egg-whites and yolks are separated in the manner used in a kitchen, the separated portions going into sterile porcelain graduates. A proportion of one whole egg to eleven egg-yolks is used and 500 cc. of this combination is obtained. The mixture, after thorough blending, is filtered through a double layer of sterile gauze into a sterile container. Ten cc. of a sterile 1 per cent solution of malachite green is then added.

The completed medium consists of equal portions of the stock and egg-yolk-malachite-green mixture. After thorough blending the medium is dispensed to sterile cotton-stoppered test tubes of 18 by 150 mm. dimensions in quantities of 10 cc. In a slanted position the medium is coagulated and sterilized by a single one-hour stay in an inspissator heated to 90° C. Further sterilization decreases the efficiency of the medium and is unnecessary if careful sterile technique is used in the preparation of the mixture.

The coagulated medium is tested for sterility by placing it in an incubator at 37° C. for forty-eight hours. The cotton stoppers are then dipped into a melted vaseline-paraffine mixture to reduce a loss of moisture. It is our experience that better growth of tubercle bacilli is obtained if all of the medium is used within a period of two weeks after it is prepared. Storage in a refrigerator is preferable to room temperature.

After the egg-yolk-potato medium had been in use for a twelve-month period the results obtained were compared to those obtained by the formerly used egg-potato medium over the previous twelve-month period. In each instance the results of the guinea pig tests were utilized as the yardstick for comparison. The data for this comparison are detailed in table 1.

The same technique for preparing the specimens for culture and animal inoculation was used throughout the study. All specimens were mixed with an

equal volume of a 5 per cent solution of sodium hydroxide. After thorough shaking the mixture is poured into sterile centrifuge tubes fitted with sterile rubber caps and digested at 37° C. for twenty minutes. Centrifugation at 3000 rpm. for twenty minutes follows. The supernatant fluid is decanted and the sediment is resuspended in a sterile buffer solution composed of 0.15 per cent KH_2PO_4, 0.35 per cent NaCl, and 0.01 per cent H_2SO_4 in distilled water. After a second centrifugation cultures and animal inoculations were made.

If a concentrate contains but few bacilli and an equal division of the sediment is made, it is conceivable that the organisms might all be in one portion. Should

TABLE 1

Results of cultures from smear-negative concentrates of sputum and from concentrates of gastric contents from tuberculous patients over two twelve-month periods. In one period egg-potato medium and in the other egg-yolk-potato medium was used. Results from guinea pig inoculation are used as the yardstick for comparison

	EGGS-POTATO MEDIUM		EGG-YOLK-POTATO MEDIUM	
	Total specimens	Per cent	Total specimens	Per cent
Sanatorium Specimens				
Total number	1,785	100	1,392	100
Total positive	320	17.9	271	19.4
Total pig-positive	307	96	222	81.9
Total culture-positive	176	55	205	75.6
Pig-positive, culture-negative	144	45	66	24.3
Pig-negative, culture-positive	13	4	49	18
Pig and culture-positive	163	51	156	57.6
"Home Office" Specimens				
Total number	312	100	365	100
Total positive	27	8.7	42	11.5
Total pig-positive	25	92.6	36	85.7
Total culture-positive	4	14.8	28	66.7
Pig-positive, culture-negative	23	85.2	14	33.8
Pig-negative, culture-positive	2	7.4	6	14.3
Pig and culture-positive	2	7.4	22	52.4

this occur, then with the method of comparison we have employed one would expect to obtain an equal number of pig-positive culture-negative and pig-negative culture-positive results, provided a medium as efficient as the pig test is used. That the bacilli were few in the specimens examined is suggested by the fact that in only half of the positive sanatorium specimens were both pig and culture positive.

The specimens obtained from the sanatorium patients were all examined promptly. The chief interest in this portion of table 1 is the results obtained with the two media. First it will be noted that approximately the same percentage of total positive results was obtained during the two periods. There was an in-

crease of 20 per cent in the total positive cultures, a decrease of 20 per cent in the pig-positive culture-negative, and an increase of 14 per cent of pig-negative culture-positive tests with the egg-yolk-potato medium. That is, this medium more nearly approximates the results of the pig test than does the egg-potato medium. The decrease from 96 to 82 per cent of total pig-positive tests is caused not by a lessened efficiency of this method, but rather by the increased efficiency of the culture medium. Note also that there is an increase of 5 per cent in the number of instances in which both pig and culture were positive. This comparison clearly indicates that the egg-yolk-potato medium approximates, although it does not equal, the guinea pig test.

The specimens under the heading "Home Office" were all gastric contents from ex-sanatorium or other tuberculous patients who were employed at the Home Office in New York City. These specimens generally required approximately twenty-four to forty-eight hours to reach this laboratory, so that the bacilli, if any, were in contact with the extracted gastric juice for some time. In this group the percentage of positive results was definitely lower than in the sanatorium group. This was to be expected, but the question arises whether the tubercle bacilli might be injured in transit to such an extent that too low a percentage of positive results would be obtained by the tests used. The marked disagreement between culture and guinea pig tests when the egg-potato medium was in use was disconcerting, to say the least. When the egg-yolk-potato medium was substituted the comparative results obtained from the culture and guinea pig tests agreed fairly closely with the results obtained with the fresh sanatorium specimens. The superiority of the egg-yolk over the egg medium is again clearly demonstrated.

Early macroscopical evidence of growth averages one week less on the egg-yolk medium in instances where but few colonies grew. Sustained bacillary growth was also more in evidence on this medium. The primary growth was predominantly smooth and glistening in contrast to the drier and rough colony formation on the whole egg medium.

COMMENTS

The original observations of Griffith and Griffith that egg-white was unsuitable while egg-yolk was a very satisfactory medium for the growth of tubercle bacilli seem to have received too little attention. Had these authors enlarged their investigations to attempt to obtain growth from material that contained very few acid-fast bacilli, an egg-yolk medium of some type would undoubtedly have become standard at an earlier date. This was clearly shown by Schwabacher (7).

In a recent article Corper and Cohn (8) have advocated a simple egg-yolk preparation for the cultivation of tubercle bacilli. To quote: "Multiple mixtures are to be avoided because they are extravagant, time consuming in preparation and redundant." We share the desire to stick to simple and easily prepared media, provided they give equal or superior results. No originality for the medium described in this article is claimed, for all of the ingredients it contains have at one time or another been utilized by other investigators. The mixture we

have detailed has certain advantages. It is as easy to prepare as a straight egg-yolk medium, once a good supply of stock is on hand. The potato adds sufficient bulk to make a firm medium. Less egg-yolk is required and there is sufficient moisture so that the medium will not become unduly dry over a long period of incubation, provided the test tubes are properly though not too thoroughly sealed. It is economical and the pale green color aids in the early identification of colony formation, as well as in deterring the growth of secondary organisms without unduly interfering with the growth of acid-fast bacilli. The glycerol is essential. The citric acid and blood powder may in time prove to be superfluous ingredients, but from our experience these substances seem to make the medium slightly more efficient. The rejected egg-white can be used to advantage in many ways.

In the past we have consistently advocated the use of both culture and guinea pig inoculation for the detection of small numbers of tubercle bacilli, since no medium we had used was as successful in demonstrating the bacilli as the guinea pig test. The egg-yolk-potato medium detailed in this report closely approximates, but does not quite equal, the guinea pig test. The difference we have found is not sufficient to further warrant the use of guinea pigs in a routine diagnostic service, from the standpoint of economy alone. The use of the animal test may now be reserved to test the pathogenicity of acid-fast bacilli, where any doubt may arise, and to detect such bacilli in cases where culture fails completely to demonstrate the organism.

With the egg-yolk-potato medium, growth of saprophytic acid-fast bacilli has been more frequently obtained. In the majority of instances these are easily distinguishable from tubercle bacilli by their more rapid growth and a variety of pigment production. On occasion a slow growing nonpigmented culture which did not quite resemble the typical growth of tubercle bacilli has been obtained. In such instances guinea pigs have been inoculated with the culture to determine the pathogenicity of the organism.

CONCLUSIONS

A relatively simple and easily prepared egg-yolk-potato medium which approximates the efficiency of guinea pig tests for the demonstration of tubercle bacilli is presented. While the guinea pig test continues to be slightly superior to the culture method the difference may be ignored, for the sake of economy, in a routine diagnostic service where large numbers of specimens are cultured for acid-fast bacilli. Use of the guinea pig may be reserved for pathogenicity tests and to aid in the demonstration of tubercle bacilli in individual cases in which the culture method fails to obtain a growth of acid-fast organisms.

CONCLUSIONES

Descríbese aquí un medio de yema de huevo y patata relativamente sencillo y fácil de preparar que se aproxima en eficacia a las pruebas en el cobayo en lo tocante a encontrar bacilos tuberculosos. Aunque la prueba en el cobayo continúa siendo ligeramente superior a los cultivos, puede ignorarse la diferencia en aras de la economía en un servicio corriente de diagnóstico en que se cultivan

muchos ejemplares en busca de bacilos ácido-resistentes. Puede reservarse el empleo del cobayo para la prueba de la patogenicidad, y para ayudar en el hallazgo de bacilos tuberculosos en casos dados en que los cultivos no obtienen colonias de microbios ácido-resistentes.

REFERENCES

(1) GRIFFITH, A. S., AND GRIFFITH, F.: Royal Com. Tuberc., 1907, 2d Int. Rep., Part II, Appendix, vol. 3: 1.

(2) LONG, E. R.: A study in fundamentals of the nutrition of the tubercle bacillus: The utilization of some amino acids and ammonium salts, Am. Rev. Tuberc., 1919, *3*, 87.

(3) PETROFF, S. A.: Some cultural studies on the tubercle bacillus, Bull. Johns Hopkins Hosp., 1915, *26*, 276.

(4) PETRAGNANI, G.: Terreno e technica per l'isolamento in cultura pura del Bidi Koch degli escreati e de altri materiali tubercolari, Atti d. r. Accad. d. Fisiocrit. in Sisena, 1926, *1*, 177.

(5) CORPER, H. J., AND COHN, M. L.: The nutrient quality of eggs for growing tubercle bacilli, Am. J. Hyg., 1933, *18*, 1.

(6) CORPER, H. J., AND UYEI, N.: The isolation of tubercle bacilli from contaminated tuberculous material, Am. Rev. Tuberc., 1927, *16*, 299.

(7) SCHWABACHER, H.: A comparison of different media for the growth of the tubercle bacillus, Tubercle, 1936, *18*, 197.

(8) CORPER, H. J., AND COHN, M. L.: Media for tubercle bacilli: An evaluation of different media for diagnostic culture of tubercle bacilli, Am. Rev. Tuberc., 1942, *46*, 560.

ACID-FAST BACILLI IN PATIENTS OF A NONTUBERCULOUS MEDICAL SERVICE[1]

E. M. MEDLAR, W. H. ORDWAY AND G. S. PESQUERA

The wide-spread distribution of acid-fast bacilli is now well known. Some types have been shown to be the aetiological agents in disease of fish, fowl and mammals. Other types, regarded as saprophytes, have been demonstrated in association with grasses, soil and some food products, such as fruits, butter and cheese. It is recognized that at times it is impossible to differentiate pathogenic from saprophytic acid-fast bacilli by morphological appearance as observed through the microscope. Distinction between the pathogenic and the saprophytic types is made more accurate by observation of cultural characteristics, but on a rare occasion appearances are deceptive. The pathogenic properties of certain strains of acid-fast bacilli can be determined if a proper type of animal is chosen for the test, but failure to demonstrate pathogenicity in animals does not necessarily prove that a so-called saprophyte bears no aetiological relationship to disease. In any laboratory where considerable numbers of specimens are examined for the presence of acid-fast bacilli the report of such bacilli in smears of sputum or other material will, on occasion, be seriously questioned by physicians. In this institution uncertainties of this nature have been settled, in part, by the demonstration of the nature of the organisms by culture and animal inoculation, and then again such studies have failed to render a decision. In some instances the acid-fast organisms have been observed in association with pulmonary disease thought to be nontuberculous in nature, and in other instances no demonstrable pulmonary lesion was evident either by physical or roentgen ray examinations. An example of this type of controversy was the demonstration of pathogenic tubercle bacilli in the gastric contents of 2 persons who had negative X-ray films of the chest. This occurred after gastric contents of 232 patients (1) with negative X-ray films of the chest had all been negative. To assemble more data on this problem it was decided to study as many as possible of the patients admitted to the nontuberculous service of this institution over a considerable period of time. These studies were made without regard to the presence or absence of pulmonary disease. Global war has ended this investigation and since a considerable volume of data has been accumulated it is deemed proper to record the results obtained.

The demonstration of acid-fast bacilli in the sputum of persons without demonstrable pulmonary disease, or with nontuberculous pulmonary lesions, is not new. A partial review of the literature will suffice to demonstrate this point. Nègre *et al.* (2) obtained a culture of chromogenic acid-fast bacilli, nonpathogenic for guinea pigs, from a patient who was gassed during World War I. Bezançon *et al.* (3) report the demonstration of tubercle bacilli in 21 persons with

[1] From the Hegeman Memorial Laboratory and the Metropolitan Life Insurance Company Sanatorium, Mount McGregor, New York.

normal X-ray films of the chest and they state: "Very slight tuberculous lesions not betrayed by any definite radiologic sign and compatible with health may, therefore, exist in the lung tissue or in or around a bronchus." Faure (4), after demonstrating pathogenic tubercle bacilli in 6 out of 67 persons with normal X-ray chest films, concludes: "As for ourselves, although this statement may hurt prevailing opinions somewhat, we are inclined to believe in the possible true existence of healthy carriers of bacilli." Dufourt (5) demonstrated nonpathogenic chromogenic acid-fast bacilli in 2 patients and states: "The presence of acid-fast baciili in the sputum should not necessarily lead to a diagnosis of tuberculosis." In discussing this paper Meyer speaks of these bacilli as "paratubercle" bacilli, a term of doubtful appropriateness. Lamache and Dutrey (6) reported the demonstration of pathogenic tubercle bacilli in 3 individuals with normal X-ray films of the chest. Their attitude toward this problem is stated as follows:

"Not long ago a positive sputum was still considered proof of pulmonary tuberculosis; now it is claimed that the examination of sputum might be a too sensitive method of investigation and its results are questioned in the presence of an apparently normal X-ray.

"This present question, after the first published reports, seems to have aroused the curiosity of many physicians: it is not only a therapeutic problem but also one of social importance, considering that each of these carriers must be regarded as a potential source of infection.

"The number of such individuals must vary in different areas. The Germans insist upon the high frequency of healthy carriers."

Terbruggen (7) states: "The occurrence of acid-fast rods in purulent bronchitis, bronchiectasis and lung abscesses is not so rare that it should preclude practical interest." Baum and Amberson (8), in a recent report, present a group of cases of pulmonary tuberculosis with complicating nontuberculous infections and include a good analysis of the literature relating to this subject. Of particular interest to our study is their discovery of active pulmonary tuberculosis in 19 out of 29 cases of pulmonary abscess with no evidence from history, clinical findings or X-ray films of the existence of tuberculosis prior to abscess formation. In a personal communication to the authors Amberson has expressed his belief that "from the later behavior of the abscess cases in which we found acid-fast bacilli, I think that all or most of these were accounted for by erosion of tubercles. In some, there was no question at all, since the tuberculosis continued to be manifest and progressive." Amberson (9) has perhaps helped to clarify this situation in the following words: "Sometimes, in retrospect, one may find in a previous roentgenogram a tiny focus which presumably may have been the precursor of the early infiltration, but without a knowledge of subsequent events the diagnosis of tubercle, rather than blood vessel, would have been highly imaginative, to say the least. Nevertheless, there is much to suggest that many or most recognizable lesions are in reality extensions from pre-existing occult foci. What we call 'early' applies only to that which is demonstrable. It is a relative term which once referred to the lesion initiating symptoms, but now to

that casting an identifiable roentgenographic shadow." It is very important to realize that unidentifiable tuberculous lesions may exist in the pulmonary field.

In a recent article Baldwin (10) reports on the recovery of chromogenic nonpathogenic acid-fast bacilli from the sputum of a patient with acute pulmonary disease. No true tubercle bacilli were demonstrated and all sputum smears were negative for acid-fast bacilli. He also obtained cultures of nonpathogenic chromogenic acid-fast bacilli from the washings of several types of fruit and vegetables and emphasized the fact that such acid-fast bacilli must frequently be ingested. This naturally complicates the interpretation of the significance of finding bacilli of this type in sputa or in gastric washings. However, it does not entirely rule out the possibility that on occasion such bacteria may have an aetiological significance, although such a relationship may be most difficult to prove.

PROGRAM AND RESULTS

The data presented in this report were obtained during the period from January, 1938 to June, 1942. The program followed was to obtain 3 twenty-four-hour sputa if the patient expectorated, or 3 consecutive fasting gastric contents within one week after a patient was admitted. The sputa were concentrated, examined by smear and then pooled for culture and guinea pig inoculation. Gastric contents were concentrated, pooled and culture and animal inoculations were done. No smear examinations of gastric contents were made since previous studies (1) had shown that such examinations gave a very low percentage of positive results and that the acid-fast bacilli observed were not necessarily tubercle bacilli. Provided coöperation of the patient could be obtained, gastric lavage was repeated at monthly intervals if the patient remained in the hospital for a considerable time. A total of 1,630 sputum smears, 626 cultures and guinea pig inoculations of sputum and 731 cultures and animal inoculations of gastric contents were done. Sputa samples were examined in 345 cases and gastric contents in 203.

It is a routine procedure in this institution to procure an initial X-ray film of the chest on all patients, and to do subsequent films on nontuberculous patients if it is deemed desirable in the management of a case. Through this procedure pulmonary lesions that would otherwise be missed are often disclosed. After the present study was terminated the clinical and X-ray interpretations of the pulmonary condition of all the patients investigated were obtained from the clinical records and the cases were separated into the following groups: group I, pulmonary field normal; group II, pulmonary lesions diagnosed as nontuberculous (cases of bronchiectasis, pneumonia, abscess, tumor, fungus infection, etc.); group III, pulmonary lesions which, because of the location and the character of the lesions, were regarded as tuberculous in nature.

It is an accepted fact that it is impossible to determine from clinical and X-ray evidence when a case with definite parenchymal lesions characteristic of a tuberculous infection is completely healed. It is also recognized that there is a

considerable number of patients who, presenting X-ray evidence of parenchymal lesions characteristic of a tuberculous infection, that show no changes by serial roentgenography, give no evidence of clinical activity. It has been our custom not to label such persons as tuberculous because of the stigma it carries. The patients included in group III come within this category. A careful survey of the records of these persons showed that there were 33 who presented pulmonary lesions characteristic of a tuberculous infection and whose serial roentgenograms revealed no changes during the hospital residence. In 15 persons there were dense parenchymal shadows that were regarded as calcified tuberculous foci. Twenty-one individuals showed areas of "haziness" in apical or subapical areas.

TABLE 1

	NUMBER AND PER CENT OF CASES	GROUP I		GROUP II		GROUP III	
		Number of cases	Per cent	Number of cases	Per cent	Number of cases	Per cent
Distribution of cases and of laboratory findings in various groups							
Total group	548 (100)	333	60.8	146	26.6	69	12.6
Negative by all methods	508 (93.5)	319	95.8	135	92.4	58	84
Positive by some method	36 (6.5)	14	4.2	11	7.6	11	16
Distribution of positive results							
Total	36 (6.5)	14	4.2	11	7.6	11	16
Smear positive							
Pig and culture negative	12 (2.2)	5	1.5	5	3.4	2	2.9
Culture positive, nonpathogenic	1 (0.2)	—	—	—	—	1	1.45
Pathogenic tubercle bacilli proved	4 (0.7)	1	0.3	2	1.4	1	1.45
Smear negative or no smear							
Pathogenic tubercle bacilli proved	11 (2.0)	6	1.8	—	—	5	7.3
Culture typical, pathogenicity not tested	1 (0.2)	1	0.3	—	—	—	—
Culture nonpathogenic	7 (1.2)	1	0.3	4	2.8	2	2.9

Had it not been for the association of a tuberculous and a nontuberculous medical service in the same institution, and for the availability of X-ray films of the chest on all patients, the presence of a tuberculous infection in these patients would not have been suspected (except, perhaps, from tuberculin tests).

Upon the basis of clinical and X-ray interpretations the 548 patients investigated were grouped as follows: group I, pulmonary field normal, 333 (60.8 per cent); group II, nontuberculous pulmonary lesions, 146 (26.6 per cent); group III, suggestive of tuberculosis, 69 (12.6 per cent). The pertinent data relative to the distribution of the cases and of the positive and negative laboratory tests are shown in table 1.

From table 1 it will be noted that acid-fast bacilli were demonstrated in all groups but the highest percentage of positive findings occurred in group III.

Of the 17 cases with positive sputum smears, 12 failed to yield culture or produce disease in the guinea pig. This will be discussed later. The distribution of positive smears among the groups is uneven with the lowest percentage in group I in which the largest number of sputum smears was examined. It will be noted also that of the 24 cases from which positive results were obtained by culture or animal inoculation only 5 had shown positive smears. It is of particular interest that 8.7 per cent of the cases in group III and 2.1 per cent in group I were shown to be discharging tubercle bacilli.

The differences between the groups are clearly indicated by the ratios presented in table 2.

TABLE 2

Ratio between groups of cases relative to positive results

	GROUP III TO GROUP I	GROUP III TO GROUP II	GROUP II TO GROUP I
Total group	3.8	2	1.8
Smear positive, cultures and pigs negative	1.9	0.85	2.3
Tubercle bacilli proved pathogenic	4.1	6	0.67
Cultures acid-fast, proved nonpathogenic	14.3	1.5	9.3

TABLE 3

Demonstration of tubercle bacilli in clinically active pulmonary tuberculosis—January, 1938 to June, 1942

STAGE OF DISEASE	NUMBER OF CASES	SPUTUM SMEARS POSITIVE		SPUTUM SMEARS NEGATIVE OR NO SPUTUM			TOTAL PER CENT POSITIVE
		Number of cases	Pathogenic bacilli demonstrated	Number of cases	Pathogenic bacilli demonstrated	No bacilli demonstrated	
Total	141	43	43	98	83	15	89.4
Minimal	53	2	2	51	42	9	83
Moderately advanced	75	30	30	45	39	6	92
Far advanced	13	11	11	2	2	—	100

Table 2 demonstrates that there is a greater frequency of acid-fast bacilli in group III when compared to the other groups. Of especial significance is the fact that pathogenic tubercle bacilli were demonstrated four times more frequently than in group I, and six times more frequently than in group II. Another fact which may be of significance is the much more frequent occurrence of nonpathogenic acid-fast bacilli in the groups with pulmonary lesions, both group II and group III, than in group I. The number of laboratory examinations done on each group was as follows: group I, 1,382; group II, 1,090; group III, 515. From the data given above it is evident that the lowest percentage of positive results was obtained in group I in which the largest number of examinations was done. Such results would hardly be expected were the positive findings due to chance or to errors of technique.

The laboratory tests on the nontuberculous cases were carried on simultaneously with similar tests on the patients diagnosed and treated as clinically active pulmonary tuberculosis. The data obtained from the tuberculous cases admitted from January, 1938 to June, 1942 may then be utilized as a "control" for the data on the nontuberculous group. During this period, 141 tuberculous cases were admitted to this institution. The data relative to the demonstration of tubercle bacilli are given in table 3.

There are two points that will bear emphasis in the group of tuberculous cases. First, all of the cases presenting positive smears of sputum were shown to have pathogenic tubercle bacilli—in contrast to the nontuberculous group. Second, 10 per cent of the tuberculous cases failed to yield tubercle bacilli despite repeated attempts to demonstrate the organisms. Thirty-one of 74 patients who expectorated failed to show a positive sputum smear, and of this group only 6 failed to yield pathogenic tubercle bacilli by repeated culture and animal inoculation. Positive results were obtained in 15 of 24 individuals who did not expectorate.

DISCUSSION

The demonstration of acid-fast bacilli in 6.5 per cent of 548 patients, with 2,987 laboratory examinations, who were considered and treated as nontuberculous, presents a problem of much significance. That the positive results obtained cannot be ascribed to chance observations or to errors of technique is clearly shown in the analysis of the data. We do not regard the results we have obtained as indicative of results that might be expected if a different group of nontuberculous individuals or of "healthy" citizens were as thoroughly investigated. The point of great significance is that, if careful search is made, acid-fast bacilli may be demonstrated in persons in whom their presence is not expected, and that such a demonstration should not be regarded as erroneous, provided the proper technique has been used.

The problem of relying upon a positive smear of sputum or of other material to diagnose a patient as tuberculous is clearly presented in this study. There were 28 instances from 17 nontuberculous persons in which acid-fast bacilli were observed in smears of sputum, and in only 4 specimens (14 per cent) were the bacilli proved to be pathogenic tubercle bacilli. In contrast to this situation, in the nontuberculous group, all of the clinically active tuberculous cases, examined during the same period, which presented sputum smears positive for acid-fast bacilli were proved to be discharging pathogenic tubercle bacilli. It may be argued that the positive smears observed in the nontuberculous group were due to errors of technique. Against such an assumption is the uneven distribution of the positive smears in the different groups. Also, 42 per cent of the tuberculous patients who expectorated failed to show acid-fast bacilli in repeated smear examinations, and only 8 per cent failed to yield pathogenic tubercle bacilli by culture and animal inoculation. The nature of the bacilli in the smear-positive sputa from the nontuberculous cases was not identified because of failure to obtain growth on culture media and because the animals

inoculated were negative in 82 per cent. That the bacilli observed in the sputum smears may be chromogenic nonpathogenic acid-fast bacilli has been proved in this study. Whenever any question arises relative to the diagnosis of tuberculous infection from a positive smear, culture and animal inoculation should always be resorted to. To quote from Pinner (11): "This enumeration suffices to show that chromogenic acid-fast bacilli occur rather frequently in human and animal tissues. This emphasizes the necessity of identifying acid-fast bacilli that may be found in diagnostically uncertain cases."

One might argue that the cases with pathogenic tubercle bacilli in group III should be placed in a group of "clinically active" tuberculosis. However, serial films showed no significant changes of the pulmonary shadows and it must be borne in mind that these cases were not proved until an intensive search for tubercle bacilli was instituted. If X-ray films of the chest are taken of all patients admitted to a hospital, evidence of tuberculous parenchymal lesions of the lungs is sure to be obtained in a certain percentage (roughly 12 per cent in 1,000 patients in this institution) and the question then arises as to the clinical significance of such findings. It has been our experience that a diagnosis of "clinical activity" is justified from the changes noted in the pulmonary shadows in serial roentgenograms, and in such instances further laboratory studies have usually revealed the presence of tubercle bacilli. Whether any of the cases proved positive in our present study will develop clinical tuberculosis is, of course, impossible to predict. It is evident that the cases included in group III are in a distinctly different category from those cases diagnosed as "clinically active" pulmonary tuberculosis in this institution. Until time has proved the significance of the positive results obtained in our present study it would seem reasonable to allow these cases to be classed as "tuberculous lesion with no apparent clinical activity." Whether any of the positive cases may be the source from which other individuals might be infected is impossible to state, but one must admit that such might be the case. A higher percentage of positive results might have been obtained in group III had it been possible to make a more protracted and intense search for tubercle bacilli. It is evident that at least a small percentage of persons in this category are in reality "open" cases of tuberculosis. Clinicians and public health officials should not wholly ignore the problem which cases similar to those included in group III present.

The demonstration of tubercle bacilli in 2 per cent of the persons whose roentgenograms of the chest were interpreted as normal may, on first thought, seem to be preposterous. Candidly considered it does not seem unreasonable. We have proved to our satisfaction that it is impossible to identify a ten-day-old tuberculous lesion in the lung of a rabbit that has been experimentally infected through the blood stream, even if the lungs in an inflated state are X-rayed out of the body to bring out details of structure that are impossible to elicit inside the thoracic cavity. Such lesions, although small, are, moreover, easily visible to the naked eye. It is also known that some cases of miliary pulmonary tuberculosis are not detectable, especially in the early stages. Likewise, small tuberculous foci not discernible in an X-ray film of the chest can be demon-

strated in X-ray films of the lungs after these have been removed from the chest. To quote again from Amberson: "What we call 'early' applies only to that which is demonstrable. It is a relative term which once referred to the lesion initiating symptoms, but now to that casting an identifiable roentgenographic shadow." It is well to recognize that undetected tuberculous lesions may exist in a lung whenever the question of reinfection or of superinfection is considered. It is also of importance to realize that tubercle bacilli may be shed from these undetected lesions.

What rôle may be played by these individuals in the spread of the disease is, of course, a moot question which can hardly be settled by forensic debate. Proof that the disease may be spread by such persons will fail to be demonstrated because, first of all, they will not be discovered unless some such similar study is undertaken. There is a tendency, in continental Europe at least, to regard individuals of this sort as "healthy carriers" of the bacilli and, if we interpret the literature correctly, this also connotes that no tuberculous lesions are present. We would agree that these persons may be in a state of excellent health, but we do not believe that there is an absence of small tuberculous foci. The tubercle bacillus being a persistent parasite tends to establish a long, rather than a transitory, residence in its host. The term "healthy carrier" does not aptly denote the real situation. It would be far better to consider the condition as an occult tuberculosis.

A satisfactory explanation for the failure of the cases in which tubercle bacilli have been demonstrated to develop a progressive infection is not available. One could surmise that in such cases a relatively high degree of resistance prevails, or that the bacilli possess a low degree of virulence. Further discussion of this situation is futile since the factors concerned with the resistance of the host and with the virulence of the infectious agent are wholly unknown. As long as the bacilli persist there remains the possibility that a lowering of resistance, or an increase of virulence of the organism, may instigate a progressive infection.

The greater frequency of association of nonpathogenic acid-fast bacilli with the groups of pulmonary lesions, tuberculous or otherwise, than with the group with normal lungs was not anticipated. Since this association is true, may it not be that these organisms are of aetiological significance in pulmonary disease? The fact that they are not pathogenic for animals ordinarily used for such tests need not preclude their being pathogenic for the individual from whom they are obtained. That bacilli of this nature may at times be ingested with fruits and vegetables, as pointed out by Baldwin, must be recognized, but this does not necessarily mean that they must always be regarded as inocuous saprophytes. It would seem that greater attention should be given to the possibility that these bacteria may be capable of instituting a disease process rather than regard them only as harmless saprophytes. To regard such bacteria as incapable of becoming pathogenic under any condition is hardly warranted.

The data presented in this report focus attention upon certain problems that are of concern to the medical profession and to public health agencies. It is well known that the source of infection for many "new" cases of tuberculosis cannot

be demonstrated even by careful surveys of "immediate contacts." Here, occult tuberculosis may perhaps play a rôle not usually appreciated. The problem of "reinfection" becomes even more obscure, for the "new" tuberculous case may have been harboring occult lesions from which the apparent disease has developed. In the light of the data presented the differentiation between "reinfection" and "superinfection" would seem to be impossible. The scope of our study is too small to warrant any general deductions relative to the frequency of undetected tuberculous lesions in a general population. The evidence presented, however, does suggest that such lesions are more common than is generally recognized. Whenever studies of the type here reported are undertaken the unreliability of sputum smears and the need for culture and animal tests are clearly indicated. A reasonable program for the management of persons with occult lesions caused by acid-fast bacilli cannot be formulated from the meager data available. There is insufficient information to enable the establishment of a sensible public health program to cope with the situation. These problems are not of immediate urgency but any program with vision must be formulated with an awareness of their existence.

SUMMARY

A study of 548 patients admitted to a medical service for nontuberculous patients revealed acid-fast bacilli by smear, culture or animal tests in 6.5 per cent of the group. Acid-fast bacilli were demonstrated in 4.2 per cent of a group of persons with normal lung fields, in 7.6 per cent of a group showing pulmonary lesions regarded as nontuberculous and in 16 per cent of a group with lesions suggestive of a tuberculous infection that revealed no apparent clinical activity. In these same groups the presence of pathogenic tubercle bacilli was proved in 2.1, 1.4 and 8.7 per cent, respectively. The characteristics of the lesions in the "tuberculous" group are discussed in the text.

Too great reliance should not be placed upon positive smears as a criterion for the diagnosis of tuberculosis in a group such as the one here reported, for of 17 persons with 27 positive smears, pathogenic tubercle bacilli were proved to be present in only 4.

Acid-fast bacilli, nonpathogenic by accepted procedures, were demonstrated in all the groups but were present with greater frequency in persons with pulmonary lesions, tuberculous or nontuberculous in nature. The possibility that these bacteria may have an aetiological significance is discussed.

The distribution of acid-fast bacilli in the three groups of cases is such that their presence can hardly be ascribed to errors of technique.

Adequate roentgenological examinations of the chest are an *a priori* requirement.

The relation of the positive results obtained to medical and public health management of infections with acid-fast bacilli is discussed.

SUMARIO

El estudio de 548 enfermos recibidos en un servicio médico para personas no tuberculosas, reveló en 6.5 por ciento del grupo bacilos ácido-resistentes en los

frotes, cultivos o pruebas en animales. Se observaron bacilos ácido-resistentes en 4.2 por ciento de un grupo de personas que mostraban campos pulmonares normales, en 7.6 por ciento de un grupo que manifestaba lesiones pulmonares consideradas como no tuberculosas y en 16 por ciento de un grupo con lesiones indicativas de una infección tuberculosa que no revelaba aparentemente actividad clínica. En esos mismos grupos se demostró la presencia de bacilos tuberculosos patógenos en 2.1, 1.4 y 8.7 por ciento respectivamente. En el texto se discuten las características de las lesiones del grupo "tuberculoso."

No debe concederse demasiada fe a los frotes positivos como pauta para el diagnóstico de tuberculosis en un grupo tal como el descrito, pues de 17 personas con 24 frotes positivos sólo en 4 se encontraron bacilos tuberculosos patógenos.

En todos los grupos se encontraron bacilos ácido-resistentes, anapatógenos conforme a los procedimientos aceptados, pero con mayor frecuencia en las personas que mostraban lesiones pulmonares y tuberculosas. Discútese la posibilidad de que esas bacterias puedan poseer importancia etiológica.

La distribución de los bacilos ácido-resistentes en los tres grupos de casos es tal que apenas puede imputarse su presencia a errores de técnica.

El adecuado examen roentgenológico del tórax constituye un requisito *a priori*.

Discútese la relación de los resultados positivos obtenidos con la asistencia médica y sanitaria de las infecciones debidas a bacilos ácido-resistentes.

We are deeply indebted to Dr. K. J. Thomson for the cases selected from his service, and to Dr. K. T. Sasano for the determination of the pathogenicity of all cultures isolated.

REFERENCES

(1) Roper, W. H., and Ordway, W. H.: Gastric lavage in adults with pulmonary tuberculosis, Am. Rev. Tuberc., 1941, *43*, 543.

(2) Nègre, L., Valtis, J., and Labernadie, V.: Paratubercle bacilli isolated from the sputum of a patient with pulmonary lesions, Compt. rend. Soc. de biol., 1931, *107*, 1054.

(3) Bezançon, F., Braun, P., and Meyer, A.: Expectorators of Koch bacilli without apparent lesions, Rev. de la tuberc., Ser. 4, 1934, *2*, 175.

(4) Faure, F.: Systematic search for bacilli in healthy individuals, Progrès méd., 1934, *62*, 1533.

(5) Dufourt, A.: Errors in diagnosis due to the presence of non-tuberculous acid-fast bacilli in the sputum, Rev. de la tuberc., Ser. 5, 1938, *4*, 232.

(6) Lamache, A., and Dutrey, M.: Valid "expectorators of tubercle bacilli," Paris méd., 1937, *1*, 357.

(7) Terbruggen, A.: On the question of the presence of acid-fast rods in bronchiectasis as cause of erroneous diagnosis of pulmonary tuberculosis, Deutsche med. Wchnschr., 1936, *62*, 1749.

(8) Baum, O. S., and Amberson, J. B.: Nontuberculous infections complicating pulmonary tuberculosis, Am. Rev. Tuberc., 1942, *45*, 243.

(9) Amberson, J. B.: Features of the early pulmonary infiltrate, Ibid., 1942, *45*, 660.

(10) Baldwin, E. R.: Nonpathogenic acid-fast bacilli, Ibid., 1942, *45*, 756.

(11) Pinner, M.: Atypical acid-fast microörganisms, Ibid., 1935, *32*, 424.

STANDARDIZATION OF SEDIMENTATION RATE[1]

J. W. CUTLER

The variety of techniques and methods for expressing sedimentation results continues to cause confusion and seriously prevents the more wide-spread adoption of this simple test in office and hospital practice. A recent example is the answer to the query in the Journal of the American Medical Association, March 6, 1943, page 797, in which five commonly used sedimentation methods are described in answer to the question, "Has any attempt at standardization of technique been made?" How is one to choose and on what grounds?

All techniques outlined in the answer, including my own, (Cutler, published in 1926) were originally developed empirically at a time when the mechanism of settling of the erythrocytes was poorly understood. As a result, these techniques have little basic merit. In each, the unit of comparison (usually the drop at the end of one hour expressed in millimeters), while it reflects the rapidity of sedimentation in a general way, fails to give an accurate idea of the rate of settling. Furthermore, an arbitrary reading at the end of a stated interval, such as one hour, also reflects anaemia because of the packing of the cells in the bottom of the tube during the first hour in rapidly settling blood. Efforts to "correct" for anaemia, as advocated by some investigators, are not only based on a wrong premise, but fail to yield consistent sedimentation findings and add greatly to the confusion. The fact that it is virtually impossible to compare the results of one method in terms of another, emphasizes the need for a satisfactory standard technique.

The object of this presentation is to discuss briefly the important factors known to have a determining influence on sedimentation rate, the basic principles involved, and to call attention to a new technique first described in the Journal of Laboratory and Clinical Medicine, December, 1940, which is based on this knowledge. This technique takes for its starting point the observation that it is the size of the rouleaux which ultimately determines the rate of settling. It is precise, simple and time-saving. The results are expressed in millimeters, are easy to interpret and need no correction for anaemia. The method embodies principles applicable to all tubes, makes a comparison of results a relatively easy matter and lends itself to standardization. To understand it, one must keep in mind the present concept of the factors believed responsible for the increased settling of the erythrocytes.

MECHANISM OF INCREASED SEDIMENTATION

It is established that the red cells do not settle as separate cells as is commonly supposed but as closely linked aggregates or rouleaux of specific size. It is known also that complete parallelism exists between the size of the rouleaux and the sinking velocity; the larger the rouleaux, the more rapid the settling and

[1] From the Henry Phipps Institute, University of Pennsylvania, Philadelphia, and the Wawa Chest Hospital, Wawa, Pennsylvania.

vice versa (figures 1 and 2). There is also proof that the arrangement of the red cells into rouleaux and the size of the rouleaux are essentially functions of the plasma and are *specific* for the different plasma, and that the size and the number of cells in suspension (anaemia) have little influence on this specificity of the plasma (Cutler, Park, and Herr).

The passive rôle of the erythrocytes in sedimentation is well illustrated by this simple experiment. When normally slowly settling cells of a healthy individual are transferred to the plasma of an individual who has a rapid sedimentation rate, they settle rapidly. Conversely, when the rapidly settling cells of the individual

FIG. 1

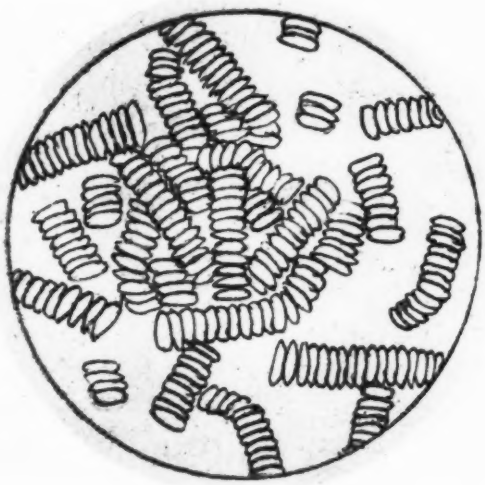

FIG. 2

FIG. 1. Rouleaux formation in slowly settling blood. The rouleaux are small and consist of relatively few cells.

FIG. 2. Rouleaux formation in rapidly settling blood. The rouleaux are large and consist of many cells. It is the increased mass of the large rouleaux that brings about rapid sedimentation. This fundamental fact underlies the technique for determining sedimentation rate described in the text.

with the marked pathological rate are transferred to the plasma of the healthy individual, they perform like normal cells and settle slowly. The significant difference is in the size of the rouleaux—small in normal plasma and large in pathological plasma—regardless of whose cells are in suspension or the presence of anaemia.

The exact nature of the changes in the plasma which bring about the formation of large rouleaux is not known but it is generally believed that the plasma proteins (fibrinogen, globulin) play a predominant rôle, probably through surface dehydration or change in the water balance on the surface of the red cells. The changes that do take place apparently are reversible and largely biophysical in character, for the rouleaux can be broken up time and again but soon reform.

On standing, however, the sedimentation phenomenon disappears with time and no settling takes place upon redistribution of the cells in the plasma for the red cells no longer form rouleaux. In such cases no discoverable quantitative changes can be demonstrated in the plasma proteins. Heat will hasten settling; cold will retard it. In general, the sedimentation phenomenon follows established laws that govern particles suspended in a viscous medium.

From the clinical standpoint, one may visualize the phenomenon of erythrocyte sedimentation in some manner as follows: Increased settling of the erythrocytes represents a change in the composition of the plasma, the result of *absorption* into the blood stream of certain products of tissue breakdown, which manifests itself in an increase in plasma fibrinogen or serum globulin or in some other alteration of the plasma not well understood. This change in plasma, in turn, brings about the physical conditions necessary for the formation of large rouleaux and hence rapid sedimentation. If this sequence of events is correct, the increased settling of red cells may well serve as an indirect measure of tissue destruction (catabolism) anywhere in the body and regardless of aetiology, provided there is sufficient absorption of those products from the site of disturbance to alter the suspension stability of the blood. This is the basis for the clinical value of sedimentation rate in medical and surgical practice.

THREE PHASES TO SEDIMENTATION PHENOMENON

Rouleaux Formation, Settling, Packing

With the above concept in mind, good sedimentation technique should represent an effort to measure simply and accurately the rate of settling (distance per unit of time) of the formed rouleaux, the ultimate factor responsible for variations in sedimentation rate. To develop such a technique, it is first necessary to study the sedimentation phenomenon as it actually takes place in the sedimentation tube by means of multiple readings at five-minute intervals by plotting the observations on graphs on which the horizontal lines represent the position of the sedimenting column of erythrocytes and the vertical lines, the intervals of time (figure 3).

Study of such graphs (graph D) reveals three phases to the sedimentation phenomenon:

(1) *Phase of aggregation or rouleaux formation:* If the technique is correct, sedimentation always starts off slowly, for it is during this slow phase that the red cells group themselves and form rouleaux. The size of the rouleaux is determined almost entirely by the composition of the plasma. Anaemia, if present, reduces the number of rouleaux that form. The more marked the anaemia, the fewer the rouleaux. But the ultimate size or mass of the rouleaux remains more or less the same, regardless of the anaemia factor. This rouleaux formation period usually varies from five to fifteen minutes, occasionally longer.

(2) *Phase of settling:* Once formed, the rouleaux settle at a uniform speed (graph B), more or less in accordance with Stokes' law of hydrodynamics, which is essentially a special application of the law of gravity—the larger the aggregate, the greater the mass, therefore, the faster the settling, and vice versa. This

gives rise to the sedimentation phenomenon. Settling during this phase may be slow (graph B) or rapid (graph D), depending upon the mass of the aggregate.

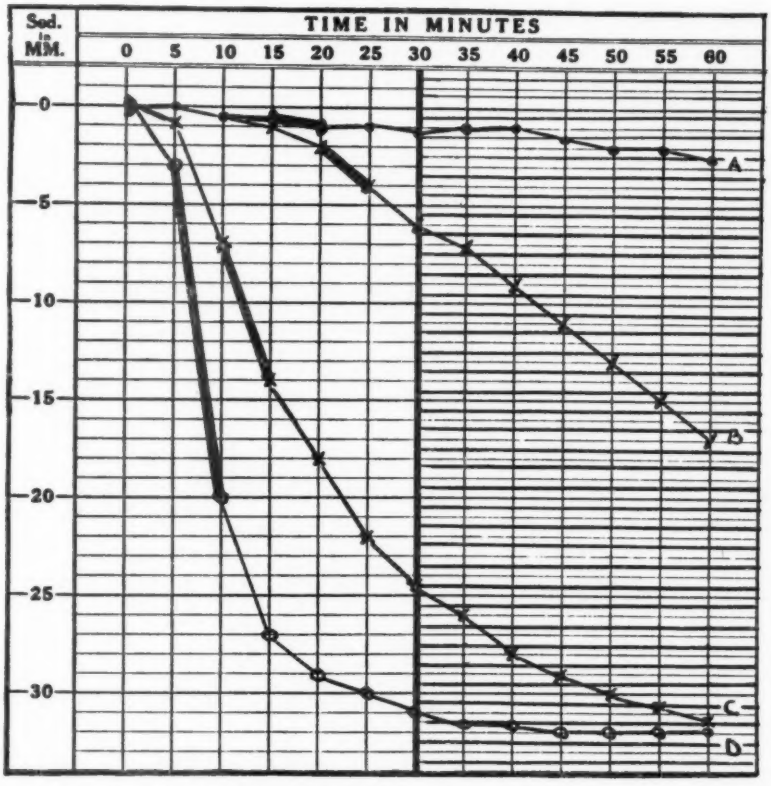

FIG. 3. Typical graphs depicting changes in erythrocyte sedimentation velocity at five-minute intervals. The record is permanent, visual, easily compared and is a check against errors in technique. Graph A, healthy person; B, subclinical tuberculosis, but active as determined by serial X-ray studies; C, pregnancy, ninth month; D, fatal carcinoma of lung.

When the retarding influence of packing is absent during the first hour, the rate of settling of the rouleaux, once formed, is fairly uniform; this is best illustrated in graph B, where the rate is 2 mm. every five minutes.

The heavy part of each graph denotes the maximum settling in any five-minute period during the hour and is a better guide to sedimentation rate than the sedimentation index (total drop at the end of one hour). Thus, graphs C and D have practically the same index (32 and 33 mm., respectively) but strikingly different maximum rates in five minutes (7 and 17 mm., respectively). Note that the maximum sedimentation rate in five minutes almost invariably occurs during the first thirty minutes and that no readings need be taken with the new technique beyond that time—shaded half of graph. The maximum settling in any five-minute period is the unit of comparison and represents the maximum sedimentation rate which the rouleaux can attain.

(3) *Phase of packing:* The rouleaux settle at their respective speeds indefinitely, depending on the length of the tube, until they reach bottom. The rouleaux that follow pack on top and the packing stage or third phase of sedimen-

tation sets in. When all rouleaux have settled tightly, sedimentation comes to a standstill. Sedimentation during the packing stage is always slow. In slowly settling blood, packing may not make its appearance during the first hour (graphs A and B). Packing always has a slowing effect on the settling rate of the rouleaux which becomes progressively greater the closer they approach those in the bottom of the tube. The entire phase of packing may be likened to the slow but orderly closing of a vertical series of accordions, those at the bottom a little more compressed than those immediately above.

It is apparent that by the time packing ensues, the sedimentation phenomenon has already taken place and that the packing of the cells represents only a rough cell volume index of the space in the tube occupied by the cells—the fewer the cells, the less space do they occupy. In rapidly settling blood, packing occurs within the hour. Because of the low cell volume index there is reflection of the associated anaemia in the increased sedimentation reading at the end of the hour. Efforts to correct for this have led to confusion. Sedimentation and anaemia are two separate phenomena and have little in common. It certainly is not possible to "correct" for anaemia and obtain consistent sedimentation rates.

The three phases, rouleaux formation, settling and packing, take place in all bloods, in all tubes and are found in all graphs. The difference is in the time required to complete the second phase or phase of settling. To determine the settling rate of the rouleaux, one should be concerned only with the phase of settling, at a time when the rouleaux are fully formed and settling at a constant velocity, uninfluenced by the period of aggregation of the red cells into rouleaux on the one hand, or their packing in the bottom of the tube on the other. By conveniently fixing the unit of time at five minutes, sedimentation rate of the settling rouleaux could then be expressed as so many millimeters per five minutes (distance per unit of time).

MAXIMUM SETTLING OF THE ROULEAUX AS THE UNIT OF COMPARISON

While one can eliminate the influence of aggregation on the settling rate of the rouleaux by the simple expedient of waiting until uniform settling has set in, it is impossible to eliminate the retarding influence of packing on sedimentation in rapidly settling blood in any tube of reasonable length, whether it be 50, 100, or 200 mm. long (figure 4). In rapidly settling blood, the slowing effect of packing on sedimentation becomes evident well within the first hour and the sedimentation rate is less in every one of the tubes mentioned than it would be normally in tubes of indefinite length. The only difference observed in tubes of varying length is in the degree of slowing.

Since the slowing effect of packing on sedimentation rate is present in all tubes and is a constant factor during the entire period of settling, but varies in degree with every length of tube, it is necessary to determine the *maximum* sedimentation rate that the rouleaux can attain in a unit of time, for example, five minutes, in a tube of fixed length. Such a unit would express the sedimentation velocity of the rouleaux at a time when it was not influenced by aggregation and least influenced by packing and may be referred to as the *maximum sedimentation*

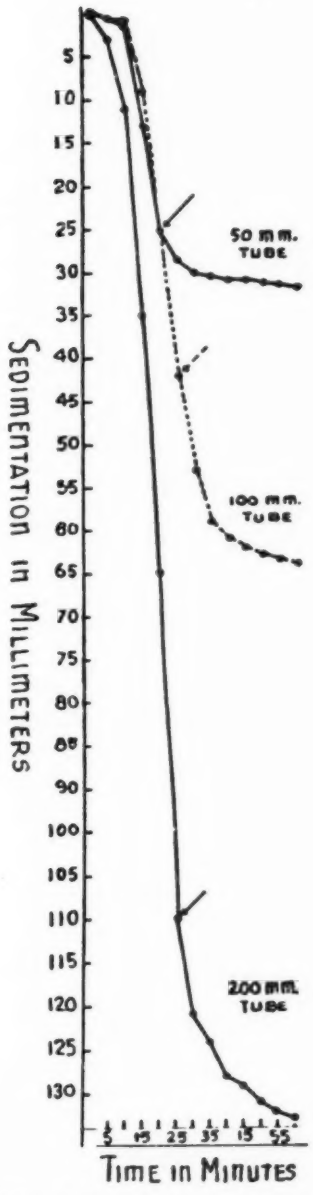

FIG. 4. The influence of packing of the cells in the bottom of the tube (packing) on the rapidity of sedimentation in tubes 50, 100 and 200 mm. long respectively, and 5 mm. internal diameter. Readings every five minutes during the first hour (same sample of blood). In the first ten or fifteen minutes settling is slow in all tubes, for it is during this period that the red cells group themselves into rouleaux. Once rouleaux are formed, however, settling becomes rapid in proportion to the size of the rouleaux. Sedimentation reaches maximum: 12 mm. in five minutes in the 50 mm. tube, between fifteen and twenty minutes; 17 mm. in five minutes in the 100 mm. tube, between twenty and twenty-five minutes; and 40 mm. in five minutes, between twenty and twenty-five minutes in the 200 mm. tube. From that point on (indicated by arrows) sedimentation in five-minute periods becomes progressively slower in each tube, because of the retarding influence of packing. Obviously the packing factor cannot be eliminated in tubes 200 mm. long and no advantage whatever is gained in employing tubes of such length. On the contrary, there are many disadvantages.

rate or *MSR*. Such a determination, for reasons mentioned above, would be independent of the anaemia factor when present, and would be a true expression of sedimentation rate in that it denotes distance per unit of time and not distance at the end of a specified time as at present.

In the Cutler tube the maximum sedimentation rate in any five minutes can be determined during the first thirty minutes of settling and no readings need be taken beyond that time. In longer tubes (200 mm. Westergren or 100 mm. Wintrobe) readings may be necessary for forty-five minutes or more before the maximum five-minute rate can be determined. Studies show that the length of the tube is also a determining factor in sedimentation rate. In the longer tubes, everything else being equal, the rouleaux are larger in direct proportion to the length of the tube but attain maximum size much later in the course of settling than in shorter tubes. Hence maximum sedimentation rate may first make its appearance during the second half hour of settling. Within certain limits the diameter of the tube is immaterial.[2]

While the maximum sedimentation rate which the rouleaux can attain in any five minutes is different in tubes of different length, and necessitates a separate scale for each tube, the different scales, however, have a definite relationship to each other and can be readily compared. Thus, compared with the 50 mm. tube, the rate is one-third faster in the 100 mm. tube, two to three times as fast in the 200 mm. tube, and three to four times faster in a 600 mm. tube. This is a ratio of approximately one-third increase in sedimentation for every 50 mm. increase in the length of the tube. Obviously, it is important to agree on a standardized sedimentation tube.

DETAILS OF PROPOSED SEDIMENTATION TECHNIQUE

The above observations are basic to an intelligent appreciation of the sedimentation technique advocated in this paper, the essential features of which are as follows:

(*1*) Cutler sedimentation tubes of 1 cc. capacity are used, graduated into 50 mm. divisions, with 0 at the 1 cc. level.[3] One-tenth of 1 cc. of 3.8 per cent sodium citrate solution (isotonic with blood, age does not matter) is aspirated into a 2 cc. syringe and blood, obtained by puncture of a suitable vein, drawn to the 1 cc. mark (for convenience, larger quantities of blood and citrate, but in the same proportion, may be used).

(*2*) After drawing back the barrel of the syringe about 1 cm., the blood and

[2] There is also proof that the Cutler tube will give sedimentation rate readings with less chance of error and with greater convenience and efficiency, inasmuch as technical factors, such as position of tube, have less effect than in longer tubes. The Cutler tube is also easier to fill and handle and has none of the disadvantages of the Westergren tube, which is essentially a pipette. It would seem justifiable, therefore, to agree on a tube of this length in an effort to standardize the technique.

[3] The Cutler tubes and racks may be obtained from Arthur H. Thomas Co., West Washington Square, Philadelphia; the special charts from Hartenstine Printing House, 206 DeKalb St., Norristown, Pennsylvania.

citrate are gently mixed by tilting the syringe backward and forward several times to safeguard against clotting.

(*3*) The contents are then emptied into the sedimentation tube up to the zero mark and the tube is placed in a special rack. This automatically insures a perpendicular position. To avoid bubbles and a blood smeared tube, the point of the needle is placed against the glass below the zero line. When the column reaches the needle tip, the needle is moved to the centre of the tube to get a clear-cut margin.[4]

(*4*) The position of the sedimenting column of erythrocytes is determined every five minutes for one-half hour. The time interval clock for announcing five-minute intervals will be found practical and time-saving, making possible sedimentation determinations with a minimum of interference with other work. The observations are recorded on charts that have been designed for this purpose. The horizontal lines on the chart represent the divisions on the tube and the vertical lines, the intervals of time.[5]

(*5*) Graphs are then constructed, which not only show the position of the sedimenting column of erythrocytes at any period of time during the first half hour, but also portray changes in velocity that occur during the process of sedimentation. This leaves a permanent, visual record, easily comprehended and readily compared, and serves as a check on technique.

(*6*) The most rapid drop in millimeters in any five-minute period during the first half hour is the maximum sedimentation rate that the rouleaux will attain in five minutes in the Cutler tube and becomes the unit of comparison.

SEDIMENTATION RATE VALUES

In the Cutler tube, a maximum settling in any five-minute period of 1 mm. or less is normal and anything more, pathological.[6] Increased rates may reach as high as 20 mm. in a five-minute period. Generally speaking, rates up to 3 mm. represent disease with relatively little absorption of those products of cellular destruction from the seat of disease which disturb the suspension stability of

[4] In large institutions where it is desirable to include the sedimentation rate in the routine blood determinations and heavy laboratory schedules make immediate examination impractical, reliable and accurate results will be obtained by distributing collecting tubes containing 0.2 cc. of 3.8 per cent sodium citrate solution and 1.8 cc. of blood syringed into this container at the same time blood is drawn for other determinations. This amount suffices for use in the 1 cc. Cutler tube. The collecting tube has two marks, one for citrate and the other for blood at the 2 cc. level. If one prefers, blood may be syringed directly into the old 5 cc. Cutler sedimentation tube containing 0.5 cc. of citrate solution. This will obviate the necessity of transferring the blood from the collecting tube to the 1 cc. sedimentation tube. Readings will be the same as in the 1 cc. tube. The test may be performed at any time within four hours of citration.

[5] See footnote 3 on page 320.

[6] The number of times the maximum rate in five-minute periods repeats during the first thirty minutes of settling, gives more detailed information on the rapidity of sedimentation —the more times it repeats the more rapid the settling. Strictly speaking, only a maximum rate of 1 mm. in five minutes which is not repeated more than twice during the half hour is normal, everything else is pathological.

the blood and, as a rule, indicate disease with slight activity; up to 8 mm., disease with moderate activity; anything higher, disease with marked activity. The normal rate of 1 mm. maximum settling in any five-minute period is broad enough to allow for all the usual physiological variations which may influence sedimentation rate, such as sex, age, menstruation, exercise and meals. Pregnancy beginning with the third month brings about an increased settling rate, which becomes more rapid as pregnancy advances.

This indicates the requirements for the precise determination and interpretation of sedimentation rate. The unit maximum sedimentation rate in any five-minute period (MSR) needs no correction for anaemia; it cannot be misunderstood for it is determined objectively.

It would seem justifiable to standardize on this technique.

SUMMARY

All sedimentation techniques described were originally developed empirically at a time when the mechanism of settling was poorly understood and fail to give an accurate idea of the rate of settling.

A new method is presented for determining sedimentation rate, based on the fundamental fact that it is the size of the rouleaux which ultimately governs rapidity of settling, and has for its object the determination of sedimentation rate at a time when the rouleaux are formed and settling at maximum velocity. This technique is precise, simple and time-saving and has none of the disadvantages of the methods commonly employed. Results are expressed in millimeters and need no correction for anaemia. The method embodies principles that are applicable to all tubes.

The essential features of the technique are as follows:

Cutler sedimentation tubes of 1 cc. capacity are used, graduated into 50 mm. divisions, with 0 at the 1 cc. level. One-tenth cubic centimeter of 3.8 per cent sodium citrate solution and 0.9 cc. of blood obtained by puncture of a suitable vein are gently mixed in a 2 cc. syringe and emptied into the sedimentation tube, and the tube is placed in a special rack. The position of the sedimenting column of erythrocytes is determined every five minutes for one-half hour and is recorded on special charts. The maximum settling in millimeters in any five minutes during the half hour is the sedimentation rate and becomes the unit of comparison. For convenience it may be referred to as MSR or maximum sedimentation rate.

A maximum settling in any five minutes of one millimeter or less is normal, anything more, pathological. Increased rates may reach as high as 20 mm. of settling in a five-minute period. Generally speaking, rates up to 3 mm. represent disease with slight activity, up to 8 mm. disease with moderate activity and anything more, disease with marked activity.

It would seem justifiable to standardize on this technique.

SUMARIO

Todas las técnicas de sedimentación descritas hasta ahora fueron elaboradas al principio empíricamente en una época en que no se comprendía bien el meca-

nismo de la sedimentación, de modo que no proporcionan una idea exacta de la velocidad de la misma.

Preséntase un nuevo método para determinar la velocidad de la sedimentación basándose en el hecho fundamental de que el tamaño de los *rouleaux*, es lo que gobierna al fin y al cabo la rapidez de la sedimentación, y que tiene por objeto determinar la velocidad de ésta cuando se forman los anillos y se depositan a su velocidad máxima. Esta técnica es precisa, sencilla y ahorra tiempo sin que adolezca de los inconvenientes de los métodos empleados habitualmente. El resultado se expresa en milímetros y no hay que corregirlos para los casos de anemia, fundándose en principios que tienen aplicación a todos los tubos.

Las características esenciales de la técnica son las siguientes: Empléense tubos de sedimentación de Cutler de 1 cc. de capacidad, graduados en divisiones de 50 mm. y en los que el cero corresponde a 1 cc. Mézclense suavemente en una jeringa de 2 cc., 0.1 cc. de solución de citrato de sodio al 3.8 por ciento y 0.9 cc. de sangre obtenida por la punción de una vena apropiada, vacíense en el tubo de sedimentación y colóquese ésta en gradilla especial. Se determina la posición de la columna de eritrocitos en vías de sedimentación cada cinco minutos por espacio de media hora y se anota en gráficas *ad hoc*. La precipitación máxima en milímetros en cualquier intervalo de cinco minutos durante la media hora constituye el índice de sedimentación y se considera como unidad de comparación. Para mayor conveniencia puede denominarse I.S.M. (en inglés M.S.R.), o índice de sedimentación máxima.

Una precipitación máxima de 1 mm. o menos en cualquier período de cinco minutos es normal; todo lo demás patológico. Los índices acelerados pueden representar hasta 20 mm. de sedimentación en un período de cinco minutos. En general, los coeficientes hasta 3 mm. representan una enfermedad de leve actividad, hasta 8 mm. de actividad moderada, y todo lo superior a esto, actividad pronunciada.

Parece justificado utilizar esta técnica para estandardización.

TUBERCULIN PATCH TEST

A Comparison with the Mantoux Intracutaneous Test

B. A. DORMER,[1] J. FRIEDLANDER,[1] F. J. WILES[1] AND R. SCHAFFER[2]

Since the introduction of the tuberculin patch test by Vollmer and Goldberger (12) in 1937, clinicians have devoted an increasing amount of attention to this undoubtedly simple method.

Speed, elimination of needle trauma and simplicity are advantages which recommend this method of tuberculin testing if it can be proved accurate.

A review of the literature reveals an astounding diversity of opinion as to the value of the test. Some authors (1, 5, 11, 12, 13, 14, 15) claim an almost complete correlation between the patch test and the Mantoux intracutaneous test; by contrast Peck and Wegman (9) showed a failure of the patch test to agree with the Mantoux test in 70 per cent of their series of 880 school children examined.

We felt that, if the test were to be used for large scale survey work in South Africa, we should satisfy ourselves as to its efficacy and, therefore, decided to study its comparative accuracy as judged against the standard Mantoux intracutaneous test in a good cross-section of our population. In view of the presence of four races in South Africa (European, colored, Bantu and Asiatic) we decided to carry out this comparison in all races.

PROCEDURE OF EXAMINATION

The Patch Test: The patch tests used were the tests devised by Vollmer and manufactured by Lederle Laboratories Inc., New York, to whom we are indebted for the supply of sufficient tests to carry out this investigation. Where only one patch test was used, it was applied on the inner side of the right forearm in adults, and between the scapulae just lateral to the spine in the children examined. Where three patch tests were applied for comparative purposes, the sites chosen were the inner side of the right forearm, the sternum and the back in the interscapular area just to the right of the spine.

The selected area was well cleaned with ether and the patch applied. Instructions were given not to get the patch wet, nor to interfere with it in any way until removed by us. After forty-eight hours the patch was removed and the test read. If there was no positive reaction the test was read again forty-eight hours later (that is, ninety-six hours after application).

The Mantoux Intracutaneous Test: Except for a group of 101 children in whom we used Koch's Old Tuberculin (0.1 cc. of 1:1000 solution) we have employed 0.1 cc. of one-third of the dilution of the second strength PPD (0.005 mg.) as the standard intracutaneous test. The reason for our using this dilution is (as we have pointed out elsewhere (3)) that, whereas the first strength gave a completely negative reaction, the second strength repeated on the same person often

[1] King George V Hospital for Tuberculosis, Durban, South Africa.
[2] Captain, S. A. M. C.

gave a very severe reaction indeed. The intracutaneous test was done on the inner side of the left forearm at the same time as the patch test was applied and read when the patch was removed. If there was any doubt about the result of the Mantoux test it was read again forty-eight hours later.

INTERPRETATIONS OF REACTIONS (3)

The Mantoux intracutaneous test was considered positive when it showed an erythematous area of induration; the patch test when it showed a follicular area with underlying erythema and induration, roughly demarcated by the square patches of tuberculin soaked filter paper. Mere redness alone without induration or follicular appearance was not considered positive.

MATERIAL USED FOR SURVEY

Our survey material is made up of six separate groups. In order to give a wider application to this study we have carried out the tests on unselected groups of the population as well as on a selected group of patients suffering from pulmonary tuberculosis; further the study has been extended to various age and racial groups. Group (*a*) is an urban Asiatic school, group (*b*) an urban Bantu school, group (*c*) an urban Bantu College (adults), group (*d*) "colored" recruits in a military camp awaiting radiography of the chest before being drafted. These are predominantly urban individuals who had been sent up from recruiting depots in various parts of the country. Group (*f*) is an urban "colored" school.

Groups (*a*), (*b*), (*c*) and (*f*) are unselected groups of the population. Group (*d*) is selected only in the respect that those with very gross disease had already been rejected at the recruiting depots by ordinary clinical methods of examination. Group (*e*) consists entirely of selected tuberculous individuals who showed both radiological and bacteriological evidence of pulmonary tuberculosis. This group comprises the four racial groups occurring in South Africa—European, "colored," Asiatic and Bantu.

RESULTS

For comparison we have decided to insert here the cumulative figures of various investigators as analyzed by Kereszturi as well as the latter's own findings (table 1) and for the sake of uniformity we have arranged our findings according to this plan. The results of our observations are presented in table 2. "The total number of tests is given, together with the distribution of the results among the four possible categories, namely, both tests negative, both tests positive, control test positive and patch test negative, control test negative and patch test positive. Computations presented in the last two columns give the information concerning the percentage of discrepancy between the two tests. The method of computing these percentages can be illustrated by the 169 tests of Vollmer in 1938. Here the control test indicated that 166 of the subjects were infected and, of these, 165 were identified by the patch test and one was not. Failure of the patch test to identify infection is therefore listed as 1 in 166, or approximately 0.5 per cent. Conversely the control test indicated that 3 of the 169 subjects

were not infected and of these one gave a positive reaction to the patch test. The false positive reactions are therefore listed as 1 in 3, or 33 per cent."

TABLE 1

TOTAL NUMBER OF CASES	BOTH TESTS NEGATIVE	BOTH TESTS POSITIVE	CONTROL POSITIVE, PATCH NEGATIVE	CONTROL NEGATIVE, PATCH POSITIVE	FALSE NEGATIVE PATCH	FALSE POSITIVE PATCH
Cumulative figures (of 10 contributors (7))						
4,162	2,228	1,586	270	78	270/1,856 15%	78/2,306 3%
Kereszturi's figures (7)						
379	237	83	31	28	31/114 27%	28/265 11%

TABLE 2

Our figures

	TOTAL NUMBER	AVERAGE AGE IN YEARS	BOTH TESTS NEGATIVE	BOTH TESTS POSITIVE	CONTROL POSITIVE, PATCH NEGATIVE	CONTROL NEGATIVE, PATCH POSITIVE	FALSE NEGATIVE PATCH	FALSE POSITIVE PATCH
(*a*) Asiatic children	179	12.7	133	43	3	—	3/46 6.52%	—
(*b*) Bantu children	105	9	66	32	7	—	7/39 17.94%	—
(*c*) Bantu adults	365	18.5	108	193	55	9	55/248 22.18%	9/117 7.69%
(*d*) Colored adults	419	25.5	92	229	86	12	86/315 27.32%	12/104 11.54%
(*e*) Tuberculosis patients (194)								
Europeans	90	37.8	3	87	—	—	—	—
Colored	27	34	2	25	—	—	—	—
Asiatic	54	30.9	4	50	—	—	—	—
Bantu	23	26.3	1	22	—	—	—	—
(*f*) Colored children	171	12	86	80	2	3	2/82 2.44%	3/89 3.37%
Grand total.....	1,433		495	761	153	24	153/842 18.17%	24/519 4.62%

Of the tuberculous group (group (*e*)), 61 patients had three patch tests applied, one on the forearm, one on the sternum and one on the back, as well as having the

Mantoux test done; 50 were positive to all four tests, 10 showed a negative patch test on the forearm but a distinctly positive one on the sternum and back, one showed a negative patch test on the sternum but a positive one on the forearm and back. The remaining 133 had a patch test applied only to the forearm. Of this number 8 did not react in the first instance. The patch was reapplied to the forearm and 2 became positive and 6 showed a positive reaction only after a third patch was applied to the back.

There were 10 patients in whom both tests were negative. The tests were repeated with the same results. All these patients had extensive bilateral tuberculosis, and the majority were in a semimoribund condition. The negative reactions might therefore quite well be accounted for by cachectic "anergy."

In group (*f*) 23 children were taken at random and had three patch tests applied in addition to having the Mantoux test; 10 were negative in all tests, 10 positive in all tests and 3 showed all tests positive except the patch test applied to the forearm.

From the point of view of the site of election for the application of the patch tests we found that the back gave the most definite reactions, more particularly in those usually accustomed to having their forearms and chests exposed. We were struck by the comparatively large number who showed a negative patch test on the forearm, although a definitely positive reaction on the back (13 out of 84 submitted to three patch tests).

CONCLUSIONS

From our investigations we have come to the conclusion that the tuberculin patch of Vollmer offers a very high degree of correlation as compared with the Mantoux intracutaneous test. Because of this, we feel that it can be employed in any large scale tuberculin testing with every confidence.

In order not to bring the patch test into disrepute we must emphasize that the technique must be carefully carried out and that the site of election should be in the interscapular area to one or the other side of the spine. This site is, as a rule, least exposed to sunshine and air, and after careful defatting of the skin with ether or acetone has in our hands proved to be the most sensitive and convenient area for patch testing. It is our feeling that most of the discrepancies that have occurred in the past may have been due to faulty technique.

We experienced no difficulty in reading the tests on the dark skin of non-Europeans.

SUMMARY

A comparative survey on 1,433 persons with the tuberculin patch test of Vollmer and the Mantoux intracutaneous test is reported. In 101 children, 0.1 cc. of 1:1000 Koch's Old Tuberculin was used for the latter test; in all others 0.1 cc. of one-third of the second strength of PPD was used.

Of this number of 1,433, there were 1,256 who had either both tests negative or both tests positive, thus giving a correlation between the two tests of 88 per cent.

In our series, 18 per cent of Mantoux positive subjects gave a negative patch test and 4.6 per cent of Mantoux negative subjects gave a positive patch test.

In the tuberculous group of 194 subjects, 10 were negative to both tests. This can be accounted for by cachectic anergy. The remainder, 184, were positive to both tests. The results in this group are striking, there being a 100 per cent correlation between the two tests.

The different figures for our "percentage false negative patch" in the various groups appear statistically inconsistent. Whether this is due to the variable human factor, to the various age groups or to difference of manufacture of the test material is difficult to assess.

SUMARIO

Preséntase una encuesta comparativa realizada en 1,433 personas a quienes se aplicaron la prueba del parche de Vollmer y la intracutirreacción de Mantoux con tuberculina. En 101 niños se utilizó para cada prueba 0.1 cc. de la tuberculina antigua de Koch al 1:1000; en todos los demás 0.1 cc. de una tercera parte de la segunda concentración de PPD.

Del citado número de 1,433, hubo 1,256 en quienes ambas reacciones resultaron bien negativas o positivas, lo cual arroja una correlación de 88 por ciento.

En esta serie, 18 por ciento de los positivos a la Mantoux resultaron negativos al parche, y 4.6 por ciento de los negativos a la Mantoux positivos al parche.

En el grupo de 194 tuberculosos, 10 fueron negativos a ambas reacciones, lo cual puede imputarse a anergia. El resto, 184, fueron positivos a ambas reacciones, siendo notable el resultado en este grupo, pues muestra una correlación de 100 por ciento entre las dos reacciones.

Las distintas cifras para el "porcentaje de seudonegativos al parche" en los varios grupos parecen incompatibles desde el punto de vista estadístico, pero es difícil determinar si esto procede del variable factor humano, de los grupos de distintas edades o de diferencias en la fabricación de las sustancias de ensayo.

REFERENCES

(1) Court, D.: Brit. M. J., April, 1939, *22*, 824.
(2) Crowe, M. P.: Ibid., February, 1942, *1*, 266.
(3) Dormer, B. A., and Friedlander, J.: Brit. J. Tuberc., 1941, *35*, 23.
(4) Fineman, A. H., and Bair, G.: Am. J. Dis. Child., 1940, *60*, 631.
(5) Hart, D. F.: Lancet, September, 1938, *2*, 609.
(6) Hughes, J. G.: J. Pediat., 1940, *16*, 171.
(7) Kereszturi, C.: Am. Rev. Tuberc., 1941, *54*, 94.
(8) Pearse, A. J., Fried, R., and Glover, V.: J. A. M. A., January, 1940, *114*, 227.
(9) Peck, E. C., and Wegman, M. E.: J. Pediat., 1939, *15*, 219.
(10) Savage, C. L.: Am. Rev. Tuberc., 1941, *43*, 527.
(11) Taylor, G.: Ibid., 1939, *40*, 236.
(12) Vollmer, H., and Goldberger, E.: Am. J. Dis. Child., 1937, *54*, 1019.
(13) Vollmer, H., and Goldberger, E.: Ibid., 1938, *56*, 584.
(14) Vollmer, H., and Goldberger, E.: Ibid., 1939, *57*, 1272.
(15) Vollmer, H., and Goldberger, E.: Ibid., 1939, *58*, 527.
(16) Editorial: Brit. M. J., July 25, 1942, p. 101.

IMMUNIZATION AGAINST TUBERCULOPROTEIN (TUBERCULIN) ANAPHYLAXIS[1,2]

H. J. CORPER AND MAURICE L. COHN

By accurate biological evaluation, it has recently been possible to differentiate specific tuberculo-immunity, specific tuberculo- (tuberculin and bacillary) allergy and specific tuberculo- (tuberculin) anaphylaxis (1, 2).

In 1939 (3), it was noted that a primary intravenous injection of about 2 mg. of tuberculoprotein sensitized guinea pigs to a lethal intravenous provocative dose (anaphylactically) of as little as about 1 mg. of tuberculoprotein. The highly concentrated filtrates resulting from the growth of tubercle bacilli on synthetic nonprotein liquid media or precipitated tuberculoproteins from these filtrates possess no appreciable primary toxicity for normal animals. In 1940, it was shown that tuberculous animals and those injected with bacilli given intravenous injections of tuberculoprotein do not die in anaphylactic shock but die protractedly from allergic intoxication. Guinea pigs sensitized with tuberculoprotein do not lose this anaphylactic sensitivity upon infection with virulent human tubercle bacilli. The two reactions, anaphylactic and allergic, can be demonstrated to coexist in the same animal (4). The tuberculoprotein sensitization (anaphylactic) can be transferred passively from about 45 per cent of the donors, while the bacillary and tuberculous (allergic) principles are never transferrable passively to normal recipients (5). In 1941 (6), we noted that the evidences obtained from the experimental study of tuberculo-anaphylaxis, tuberculo-allergy and specific tuberculo-immunity would seem to question whether the active constituent of *in vitro* natural filtrate (tuberculoprotein) from the growth of tubercle bacilli is liberated *in vivo*. In spite of this, desensitization of bacillary tuberculo- (tuberculin) allergically sensitized animals, prepared with either avirulent or virulent human tubercle bacilli, can be accomplished by appropriate treatment with natural tuberculo-filtrate (tuberculoprotein—tuberculin) when it is used in relatively small primarily nontoxic amounts. The animals thus prepared do not show a local specific skin reaction to natural filtrate (tuberculin) and are likewise protected against a lethal general tuberculo- (tuberculin) allergic shock. The protective materials are contained in the blood of appropriately desensitized (tuberculin) tuberculo-allergic animals, and this protection can be transferred to a tuberculo- (tuberculin) allergic sensitive animal with the blood from a desensitized (with tuberculin) tuberculo-allergic animal. In 1942 (7), the results of further studies revealed that tuberculo-anaphylactic hypersensitiveness in mother guinea pigs, produced by the injection of tuberculoprotein, is regularly transferred to offspring born for over a year after sensitization of the mother. The tuberculo-anaphylactic hypersensitiveness may persist in the young in demonstrable form up to at least three months after birth. Tuberculo- (tuber-

[1] From the Research Department, National Jewish Hospital, Denver, Colorado.

[2] This study was aided by the Jacques Labarrere Fund for Tuberculosis Research.

culin) allergic hypersensitiveness in tuberculous mother guinea pigs produced by infection is not transferred to the offspring. In 1940 (5), we reported that "as little as the equivalent of 0.1 mg. of tuberculoprotein on single intravenous injection and 0.000,9 mg. total, divided into nine weekly intracutaneous injections of 0.000,1 mg. of tuberculoprotein equivalent, sensitized the guinea pigs to fatal anaphylactic shock." Thus these injections at weekly intervals sensitized to anaphylaxis and the logical deduction would be that desensitization to anaphylactic shock with tuberculoprotein would not be feasible. However, this need not follow necessarily; and since it was proved possible to desensitize to tuberculo-(tuberculin) allergic intoxication by appropriate dosage and spacing of injections, it seemed likely that this factor possessed by tuberculin might also be present in tuberculin anaphylaxis. Therefore, various spacing of intravenous tuberculin injections was tried for the purpose of exhausting the possibilities of desensitization to tuberculin anaphylactic shock. The following typical experiment serves to elucidate this problem of desensitization to tuberculin anaphylactic shock.

A series of guinea pigs was given intravenous injections of 5 cc. of natural Seitz filtrate (containing a total of 6.2 mg. of tuberculoprotein); twenty-six days later, the first intravenous desensitization injection of the equivalent of 0.1 cc. of natural filtrate (0.07 mg. tuberculoprotein) was given; then eight more daily injections of tuberculoprotein (as natural filtrate) were given intravenously in 0.07 mg., 0.14 mg., 0.36 mg., 0.72 mg., 1.08 mg., 1.44 mg., 1.56 mg. and 3.9 mg. amounts. Six days after the last injection, guinea pigs thus prepared gave no reaction following the intravenous injection of 2.5 cc. natural filtrate (1.9 mg. tuberculoprotein), nor two weeks later following 5 cc. natural filtrate (3.4 mg. tuberculoprotein), nor five weeks later following 5 cc. natural filtrate (3.4 mg. tuberculoprotein), nor two months after the previous injection to 5 cc. natural filtrate (3.4 mg. tuberculoprotein). Another series of guinea pigs given the daily desensitizing injections as above gave no reactions or only slight reactions as follows: three days after the last daily desensitizing reaction, following the intravenous injection of 5 cc. natural filtrate (3.4 mg. tuberculoprotein), a slight reaction with recovery occurred; then ten days later, no reaction followed the intravenous injection of 5 cc. natural filtrate (6.2 mg. tuberculoprotein); and three weeks after this injection, no reaction occurred following the intravenous injection of 5 cc. natural filtrate (3.4 mg. tuberculoprotein); while the third injection again resulted in a mild reaction in some guinea pigs, following the intravenous injection (four weeks after the foregoing injection) of 5 cc. natural filtrate (3.4 mg. tuberculoprotein). Likewise, reactions failed to occur or were mild at the following intervals: two months, (3.4 mg. tuberculoprotein) negative; three months, (3.4 mg. tuberculoprotein) slight reaction; three months, (6.2 mg. tuberculoprotein) negative; three months, (6.2 mg. tuberculoprotein) slight reaction; and finally after nine months, (6.2 mg. tuberculoprotein) moderate reaction with a few acute lethal results.

Controls not immunized against anaphylactic shock with tuberculoprotein following the primary tuberculoprotein sensitization succumb to acute anaphylactic death after the intravenous injection of 1 to 2 cc. filtrate (0.6 mg. to 1.2 mg. tuberculoprotein) at any time two to three weeks after sensitization and for

at least one year. It is evident from these experiments that tuberculoprotein immunization is possible against acute tuberculoprotein anaphylactic intoxication in a guinea pig appropriately sensitized to tuberculoprotein anaphylaxis.

In further experiments in which the immunizing tuberculoprotein was given intravenously at bidaily intervals instead of daily intervals, immunization was likewise possible, in contrast to the fact that weekly injections failed to immunize satisfactorily as previously reported. These experiments suggest a mechanism whereby small repeated increasing injections of tuberculoprotein appear to neutralize or exhaust the substance that account for the anaphylactic intoxication and to reach a toxic limit only when neutralization or exhaustion does not take place within a week's time. The intoxication or intoxicating substance does not appear to be the tuberculoprotein itself but may be a substance formed slowly by the body and which requires the new injection of tuberculoprotein to consummate the toxic material. The amount of tuberculoprotein, whether in excess or just sufficient, determines the outcome only insofar as the body is able to produce the unknown other part of the intoxicating substance.

In order to elucidate further this problem of immunizing against tuberculin anaphylactic shock, the following experiments were performed. In the first set of experiments, guinea pigs were sensitized to anaphylactic shock by the intravenous injection of 6.2 mg. tuberculoprotein (as natural filtrate) and then were immunized against anaphylactic shock by giving daily intravenous injections of 0.08, 0.16, 0.4, 0.6, 1.2, 2.5 and 6.2 mg., respectively, which were begun six weeks after the primary sensitizing injection of tuberculoprotein. The citrated whole blood from these immunized animals, taken from the heart in 10 cc. amounts, was injected intravenously into normal guinea pigs. Twenty-four hours later the latter guinea pigs were given an intravenous injection of 5 cc. (3.0 mg. tuberculoprotein) natural Seitz filtrate and no reaction occurred. This amount of Seitz filtrate would normally produce tuberculoprotein hypersensitiveness in a normal guinea pig, but the foregoing guinea pigs tested three to four weeks after the natural filtrate injections for anaphylactic hypersensitiveness to tuberculoprotein failed to react. This would suggest that the injection of the tuberculin immune serum had so altered the mechanism that protection occurred temporarily. Yet when these same guinea pigs were given an intravenous injection of tuberculoprotein (natural filtrate) after an interval exceeding three months from the last tuberculoprotein injection, a lethal anaphylactic shock resulted.

In another experiment, tuberculoprotein immune citrated whole blood was transferred to tuberculoprotein (anaphylactic shock) hypersensitive guinea pigs; and, at various intervals thereafter, they were tested for lethal shock by means of an intravenous injection of tuberculoprotein (1 to 5 mg.) as natural filtrate. The guinea pigs tested after thirty minutes to seventy-two hours died of acute anaphylaxis, indicating that the tuberculin immune blood did not possess the power to protect an anaphylactic hypersensitive guinea pig, even though this blood prevented sensitization to lethal anaphylaxis as shown above.

In a final experiment, tuberculin nonimmune and immune bloods were mixed with tuberculoprotein (tuberculin) *in vitro*, and this mixture was then injected into anaphylactically hypersensitive guinea pigs. In the first series of this

experiment, 10 cc. of citrated whole blood from a tuberculoprotein hypersensitive guinea pig was mixed with 5 cc. natural filtrate (5.3 mg. tuberculoprotein) and allowed to stand ten minutes at room temperature. On injection of only 2 cc. into a hypersensitive animal, the guinea pig died in acute anaphylactic shock. Even up to four hours' contact of the tuberculoprotein and blood did not alter the result. The foregoing experiment was repeated with 10 cc. of citrated whole blood, obtained from a tuberculoprotein immunized guinea pig mixed with 5 cc. natural filtrate (4.0 mg. tuberculoprotein); although the mixture remained in contact for from ten minutes to four hours in various tests, lethal anaphylactic tuberculin shock resulted when this mixture was injected intravenously into a tuberculoprotein (anaphylactically) hypersensitive guinea pig.

It would appear from the foregoing experiments that treatment of tuberculin (tuberculoprotein) with the citrated blood of either tuberculoprotein anaphylactically hypersensitive guinea pigs or the citrated blood from hypersensitive guinea pigs, immunized against lethal anaphylactic shock by appropriate spacing and dosage of tuberculoprotein (tuberculin), exerted no appreciable effect *in vitro* upon the property of this tuberculoprotein (tuberculin) to elicit fatal tuberculoprotein (tuberculin) anaphylactic shock in tuberculoprotein anaphylactically hypersensitive guinea pigs. These experiments serve to elucidate tuberculoprotein anaphylaxis and should aid in the ultimate explanation of its mechanism.

SUMMARY AND CONCLUSIONS

1. It has been shown that four independent biological reactions to tubercle bacilli and their natural products occur which are important in the evaluation of tuberculosis. These are specific tuberculo-immunity, specific tuberculobacillary-allergy, specific tuberculin allergy, and tuberculoprotein (tuberculin) anaphylaxis.

2. Tuberculoprotein (tuberculin) anaphylactic hypersensitiveness is produced in guinea pigs by relatively small amounts of tuberculoprotein (tuberculin), and lethal anaphylactic shock results from an intravenous injection of the same tuberculoprotein (tuberculin) any time two to three weeks after sensitization.

3. Proper repeated and spaced intravenous injections of tuberculoprotein (tuberculin) suffice to immunize guinea pigs against an otherwise lethal tuberculoprotein (tuberculin) anaphylactic shock.

4. Passive transfer of citrated blood of tuberculin immune guinea pigs to normal animals prevented tuberculoprotein (tuberculin) sensitization to tuberculin anaphylactic shock.

5. Passive transfer of citrated whole blood, of immune or anaphylactic hypersensitive guinea pigs with or without the addition of tuberculoprotein (tuberculin), failed to protect tuberculin hypersensitive guinea pigs from the effect of the lethal tuberculin anaphylactic shock.

SUMARIO Y CONCLUSIONES

1. Se ha demostrado que cuatro reacciones biológicas independientes a los bacilos tuberculosos y sus productos naturales revisten importancia en la avalua-

ción de la tuberculosis, y son: la tubérculo-inmunidad específica, la alergia tubérculo-bacilar específica, la alergia a la tuberculina específica, y la anafilaxia a la tubérculoproteína (tuberculina).

2. En los cobayos se produce hipersensitividad anafiláctica a la tubérculoproteína (tuberculina) con cantidades relativamente pequeñas de tubérculoproteína (tuberculina), y la inyección intravenosa de la misma tubérculoproteína (tuberculina) produce choque anafiláctico letal en cualquier momento de dos a tres semanas después de la sensibilización.

3. Las inyecciones intravenosas repetidas y debidamente espaciadas de tubérculoproteína (tuberculina) bastan para inmunizar al cobayo contra un choque anafiláctico a la tubérculoproteína (tuberculina), que de otra manera resultaría letal.

4. El pase pasivo de sangre citratada de cobayos inmunes a la tuberculina, a los animales normales, impidió la sensibilización con tubérculoproteína (tuberculina) al choque anafiláctico producido por la tuberculina.

5. El pase pasivo de sangre íntegra citratada de cobayos hipersensibles, inmunes o anafilácticos con o sin la adición de tubérculoproteína (tuberculina) no protegió a los cobayos hipersensibles a la tuberculina contra el efecto del choque anafiláctico letal por tuberculina.

REFERENCES

(1) Corper, H. J.: Analysis of the tubercle bacillus and its natural products by immune, allergic and anaphylactic tests, J. Infect. Dis., 1940, *66*, 22.

(2) Corper, H. J.: Bacillary and tuberculin allergy and their relation to specific tuberculosis immunity, Yale J. Biol. & Med., 1943, *15*, 373.

(3) Corper, H. J., and Cohn, Maurice L.: The effects of tuberculoprotein: A quantitative study, J. A. M. A., 1939, *112*, 403.

(4) Corper, H. J., and Cohn, Maurice L.: Intoxication in tuberculosis, Am. Rev. Tuberc., 1940, *41*, 71.

(5) Corper, H. J., Cohn, Maurice L., and Damerow, A. P.: Relations between specific immunity, allergy and anaphylaxis in tuberculosis, Am. J. Clin. Path., 1940, *10*, 361.

(6) Corper, H. J., Damerow, A. P., and Cohn, Maurice L.: Tuberculoprotein desensitization and tuberculosis, Ibid., 1941, *11*, 463.

(7) Corper, H. J., and Clark, C.: Congenital tuberculin hypersensitiveness and specific tuberculo-allergic immunity, Am. Rev. Tuberc., 1942, *46*, 309.

PNEUMOPERITONEUM[1, 2]

Its Scope and Limitations in the Treatment of Pulmonary Tuberculosis

I. ELLIS RUDMAN

The instillation of sterilized air, oxygen or nitrogen into the abdominal cavity has been used for a good many years as an aid in the diagnosis of obscure abdominal lesions and for the treatment of intestinal tuberculosis. Its adaptation to the treatment of pulmonary tuberculosis is of more recent origin.

A voluminous literature has accumulated on this subject in the last few years. The reports on the efficacy of this form of treatment run the whole gamut of enthusiasm to pessimism. Banyai (1) gave a review of 220 cases in which pneumoperitoneum was employed for the treatment of pulmonary tuberculosis. His results, on the whole, were very encouraging. About the same time that his article appeared, Stokes (2) gave a careful analysis of his observations in 41 cases treated by this method. He states that, after three years of observation, one case can be considered as arrested, one apparently arrested, 5 improved, 15 unimproved or made worse and 19 died. His results were poor, but consideration must be given to the fact that the cases he chose for this form of treatment were far advanced. It is, therefore, somewhat futile to draw conclusions as to the value of pneumoperitoneum in the treatment of pulmonary tuberculosis unless we give due regard to the type of case in which it is employed.

Pneumoperitoneum is reserved for patients in whom artificial pneumothorax or other orthodox forms of collapse therapy cannot be employed.

The advocates of pneumoperitoneum claim that the beneficial results brought about are due to:

1: Elevation of both hemidiaphragms giving rest to the diseased lung.
2: Lymph stasis, which in turn promotes tissue fibrosis.
3: Pulmonary congestion and anoxaemia which in turn inhibit the growth of tubercle bacilli in the tissues and hasten reparative processes. It is supposed to affect especially basilar pathology.

However, these theoretical considerations do not always work out in practice.

(*a*) Mobility of the diaphragm is impaired or limited but rarely abolished, even though large amounts of air are instilled in the abdominal cavity and intra-abdominal pressure is raised to a high degree.

(*b*) In advanced cases, subdiaphragmatic adhesions limit the rise of the diaphragm.

(*c*) In advanced cases, because of the fibrotic character of the lesion and its resistance to compression, even though a hiatus is created by the pneumoperitoneum showing the presence of air between the liver and the diaphragm, and

[1] From the Division of Tuberculosis, Memorial Hospital, Roxborough, Philadelphia, Pennsylvania.

[2] Read at the seventh annual meeting of the American Academy of Tuberculosis Physicians at the Hotel Dennis, Atlantic City, New Jersey, June 9, 1942.

between the stomach and diaphragm, the actual rise of the diaphragm is more apparent than real. The intraäbdominal pressure causes a downward displacement of the abdominal viscera.

(*d*) Extreme pressure affects the abdominal viscera and interferes with the patient's intake of food and hastens the clinical downward trend. Any attempt to make the pneumoperitoneum effective and to stretch adhesions by the increase of intraäbdominal pressure, causes excruciating shoulder girdle pains in many advanced cases.

But while in the advanced cases the presence of subdiaphragmatic adhesions, the extent of the lesions in the lung tissue and tonus of the diaphragm may nullify whatever benefits there are to be obtained from pneumoperitoneum, a far different picture and more salubrious results are brought about when pneumoperitoneum is used in the early or moderately advanced case to enhance the value of phrenic neurectomy. No matter how poor the results are from a phrenic operation, the use of pneumoperitoneum greatly enhances its value. To Joanides and Schlack (3) belongs the credit for first advocating the use of pneumoperitoneum as a supplementary measure to phrenic neurectomy.

Pneumoperitoneum is a far more formidable procedure than pneumothorax, therefore the procedure of pneumoperitoneum should be done with great caution and care. The use of nitrogen has been resorted to as the agent to be used for pneumoperitoneum for the reason that this gas is more slowly absorbed and refills are less frequently required. The skin sterilization is done on a small area on the abdominal wall with meticulous care. Tincture of green soap is used followed by alcohol and then the area selected is painted with tincture of metaphen. The point chosen for the insertion of the needle is about one inch above and to the left of the umbilicus. The skin is infiltrated with 2 per cent procaine hydrochloride solution. The tubing is attached to the pneumothorax apparatus in the usual way and to the free end of the tubing is attached a three-way petcock. A 5 cc. luer syringe partly filled with procaine solution is attached to the petcock and a Vim 19 gauge $2\frac{1}{2}$ inch needle is used. Insertion of the needle through the abdominal wall is made gradually. There is often a sensation in the hands of the operator that tells him when the peritoneum is punctured. To make certain that the needle has traversed the abdominal wall and is in the peritoneal space, a minute amount of nitrogen is allowed to go through the tubing and reading is made by means of the water manometer. If the needle is in the peritoneal cavity, there is very little movement of the water in the manometer but, if the needle is still in the abdominal wall, there is a sudden rise of the water level on the positive side. Further insertion of the needle is then permissible and again if a reading is made, it will show a sudden drop of the manometric readings to zero or to a minus one or a minus two. We are then ready to allow more nitrogen to enter the abdominal cavity. As a rule, 500 or 600 cc. of nitrogen is used for the initial instillation.

The drawbacks to the administration of pneumoperitoneum are that:

(*a*) The usual water manometer is not sufficiently sensitive to give us an accurate gauge of the variation and fluctuation of the intraäbdominal pressure.

(*b*) Even the most careful operator will frequently cause infiltration of the abdominal wall with air or nitrogen and a resulting subcutaneous emphysema. A severe infiltration of air in the retroperitoneal tissue and its gravitation to the mediastinum has been reported to me by Ellison (4). Though no fatality resulted, this patient was extremely ill for a time.

(*c*) Hobby (5) reported that he gathered from the literature 4 cases of air embolism, 4 cases of injection of air into the spleen and one death due to peritonitis.

(*d*) Trimble and others (6) have made a study of the local effects of long continued pneumoperitoneum and reported that, in their opinion, there were definite signs of peritoneal irritation and that the formation of ascites, occurring during the course of treatment, is analogous to the formation of an effusion in the course of pneumothorax treatment. However, the need for aspiration of fluid from the abdominal cavity rarely arises.

The place of pneumoperitoneum in the treatment of pulmonary tuberculosis is now at the stage where pneumothorax was twenty-five years ago. Its use as a last resort measure and the paucity of results obtained in such cases will eventually cause this method to be regarded with disfavor and probably thrown into discard. Pneumoperitoneum cannot be expected to close thick-walled cavities or be of any value in the far advanced case where the spread is generalized in both pulmonary areas, any more than pneumothorax can be utilized in such cases. To resort to pneumoperitoneum where symphysis of the pleura prevents the possibility of pneumothorax or other forms of collapse therapy would only be an unnecessary expenditure of effort and no lasting benefit to the patient. The indications for pneumoperitoneum must be clear-cut and the cases properly selected. With this in mind, I have refrained from giving any statistical data on a number of cases treated and the results obtained, but show a series of cases in which pneumoperitoneum is of value and others in which it is valueless.

Pneumoperitoneum as a Palliative Measure

Case 1—Mr. S.: Age twenty-two. Mr. S. was employed in a CC Camp when he was taken ill in the spring of 1938. His condition was diagnosed as a tuberculous pneumonia and he was admitted to a state sanatorium where he remained until June, 1939. At that time, physical examination, confirmed by X-ray films, showed a far advanced caseous pneumonic cavitary tuberculosis. The whole right upper lobe was excavated. The rest of the right pulmonary field showed dense pneumonic infiltration. The left lower lobe contained a solid tuberculous pneumonic process. Figure 1 shows the results obtained after the institution of pneumoperitoneum. Pneumoperitoneum was instituted for the sole purpose of bringing about some amelioration of the cough and the difficulty the patient had in bringing up expectoration. No hope was engendered that this procedure would in any way alter the downward course in this case. However, as a palliative measure, it was of little or no value. It seems to me that to make the life of the far advanced case more bearable we have at our command measures that are far less heroic and less drastic than pneumoperitoneum.

Pneumoperitoneum Used to Stop a Severe Pulmonary Haemorrhage

Case 2—Mr. T.: Age forty-four. This man, when first seen in 1936, had a moderately advanced pulmonary tuberculosis. The right upper lobe showed a fibrocavitary lesion. The sputum was positive for tubercle bacilli. There was frequent haemoptysis. Pneumothorax was instituted on the right side but soon abandoned because it was limited in extent and produced little benefit. A phrenicectomy was done on the right side on October 28, 1936. Though the rise of the right hemidiaphragm was limited in extent, the results were very gratifying. He gained in weight and strength. Sputum conversion occurred. In the interval between 1936 and 1940, he led a life of moderate activity. In the spring of 1941, there was a gradual return of cough and expectoration and loss of strength and vitality. On the 1st of July, 1941, he had a very copious pulmonary haemorrhage. It was hoped that, since the paralysis of the right hemidiaphragm still existed, the pulmonary haemorrhage could be controlled by the institution of pneumoperitoneum. Although a successful pneumoperitoneum was established, the results were disappointing since the thick cavity walls were not affected by the subdiaphragmatic pressure. The pulmonary haemorrhage was uncontrolled and the patient died.

Pneumoperitoneum Used in Preparation of the Patient for Thoracoplasty

Case 3—Miss J.: Age twenty-two. The history of this case begins in 1936. At that time she had an acute exudative process in the right upper lobe. Several attempts at establishing pneumothorax on the right side proved unsuccessful. She was then sent to a state sanatorium where she remained until 1939. In spite of the fact that she had complete bed-rest and excellent care, the lesion went on to cavitation. Figure 2 shows the appearance of the lesion on April 8, 1939. Two large cavities can be seen in the right upper lobe and two smaller cavities in the right middle lobe. She was running a hectic course, characterized by night sweats and afternoon elevation of temperature. She was losing weight steadily. The establishment of pneumoperitoneum showed that the right hemidiaphragm was not bound down by any adhesions, but its rise was limited in extent. There was some improvement in the patient's general condition and, although the cavities became smaller in size, the change was only slight as seen in Figure 3. However, after a phrenicectomy was done and the pneumoperitoneum continued, the diaphragm rose to the level of the third rib. The lowest cavities were obliterated. Figure 4 shows only two cavities, much smaller than those noted when this patient first came to our attention. However, our failure to close the remaining cavities in the right upper lobe forced us to abandon pneumoperitoneum. The general physical condition of the patient was now so much improved that thoracoplasty could be considered. The stopping of pneumoperitoneum refills caused a descent of the hemidiaphragm and the cavities first seen in 1939 became apparent again, as shown in figure 5. A first stage thoracoplasty was done in which the first three ribs were removed on the right side. Because of circumstances beyond our control, an unusually long interval ensued between the first and second stage, which was done in August, 1940. Figure 6 shows the end-results obtained after removal of the fourth, fifth, sixth and seventh ribs. It is evident that pneumoperitoneum in this case aided materially in reducing activity on the right side and in making the patient suitable for thoracoplasty in less time than could have been accomplished by bed-rest alone.

Pneumoperitoneum to Increase the Effect of Phrenic Neurectomy

Case 4—Mrs. H.: Age twenty-eight. This case illustrates best of all the benefits to be derived from pneumoperitoneum in a suitable, well selected case. The history of this case

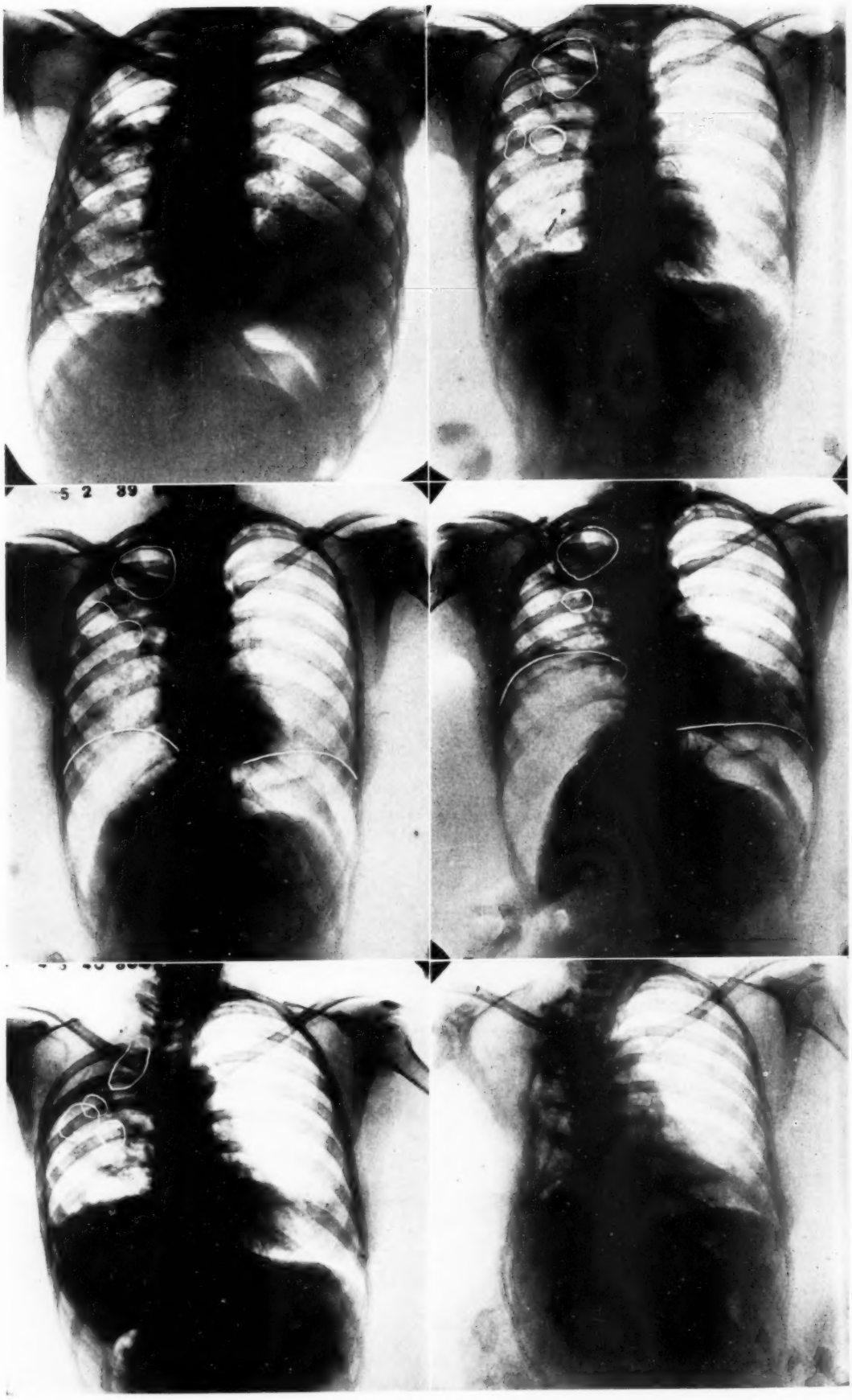

PLATE I

begins in June, 1940, when she was admitted to a Philadelphia hospital for the treatment of pulmonary tuberculosis. At that time she had an acute exudative cavitary lesion in the left upper lobe and a contralateral spread in the subclavicular area. Pneumothorax was established soon after her admission to the hospital but, because of the presence of numerous adhesions, an effective collapse was not obtained. Thoracoscopy was done and the adhesions were found to be inoperable. Pneumothorax was abandoned and the lung was allowed to reëxpand. She remained nine months at this institution. The course was steadily downward. There was continuous loss of weight and strength. She ran a hectic, febrile course. Thoracoplasty was contraindicated because of the active character of the lesion and the spread to the contralateral side. Extrapleural pneumothorax was considered, but because of the location of the cavity and its position near the periphery of the lung, it was considered inadvisable to carry out this procedure. On June 28, 1941, she was admitted to the Rush Hospital. Physical examination, confirmed by X-ray examination, showed a large cavity in the left apex to the level of the third rib anteriorly, located near the periphery of the lung and about 10 by 8 cm. in diameter. The rest of the pulmonary area showed scattered infiltration. The right upper lobe showed a fairly extensive lesion, fibrocaseous in character. A phrenicectomy was done on the left side on July 11, 1941. The diaphragmatic rise was limited in extent and hardly affected the cavity in the left upper lobe. The dome of the diaphragm reached to the level of the eighth rib posteriorly. On August 20, pneumoperitoneum was instituted with the hope of making the diaphragmatic rise more effective. The diaphragm was kept at the level of the sixth rib posteriorly with the instillation of 600 to 700 cc. of nitrogen at weekly intervals. The right hemidiaphragm was also elevated but to a very slight degree. The effect on the cavity in the left upper lobe was noted after two months of treatment by pneumoperitoneum. The cavity became more shallow, the edges more sharply defined and smaller in circumference. On June 16, 1942, the film showed a gradual clearing of the infiltrative process in the left pulmonary area with the complete obliteration of the cavity previously noted in the left upper lobe. Improvement also was noted in the process on the

---

FIG. 1 (Upper left). Case 1. Mr. S. June 13, 1939. Advanced pulmonary tuberculosis, showing dense infiltration throughout the right pulmonary area and a cavity occupying almost all of the right upper lobe. A dense pneumonic process is present in the left lower lobe.

FIG. 2 (Upper right). Case 3. Miss J. April 8, 1939. This film shows the appearance of the lesion in 1939. In spite of almost continuous bed-rest, the condition went on to cavitation and we have here a fibrocaseous lesion affecting the right upper and middle lobes. Four distinct cavities are visible.

FIG. 3 (Middle left). Case 3. Miss J. May 2, 1939. The institution of pneumoperitoneum in this case caused the elevation of both hemidiaphragms, slightly more so on the right side. Pneumoperitoneum caused obliteration of the lower cavities and a slight reduction in the size of the others.

FIG. 4 (Middle right). Case 3. Miss J. October 25, 1939. The addition of a phrenicectomy in this case on the right side aided materially in the diaphragmatic rise. In this film, only two cavities are visible in the right upper lobe.

FIG. 5 (Bottom left). Case 3. Miss J. April 3, 1940. Pneumoperitoneum abandoned. The stopping of the pneumoperitoneum refills caused a descent of the hemidiaphragm and the cavities first seen in 1939 became apparent again. This film shows a first-stage thoracoplasty in which the first three ribs were removed on the right side.

FIG. 6 (Bottom right). Case 3. Miss J. August 3, 1940. This film shows the end-result of a second stage thoracoplasty in which the fourth, fifth, sixth and seventh ribs were removed.

right side. Sputum conversion took place. The patient had gained by that time nearly forty pounds in weight. On March 24, 1943, a pneumoperitoneum refill was given for the last time. Though it is too soon to state the permanency of results in this case, so far there has been no reactivation of the process or return of cavitation.

Limited Value of Pneumoperitoneum as the Sole Therapeutic Measure

Case 5—Mr. B.: Age thirty-four. Symptoms began with a "chest cold" in January, 1941. There was slight cough and very little expectoration. The main complaint was excessive fatigue and nervousness. There was a history of a severe dry pleurisy on the right side four years previously. On February 13, 1941, physical examination, confirmed by X-ray examination revealed an acute exudative process in the right upper lobe with a thin-walled cavity at the level of the second rib anteriorly in the midclavicular line. Pneumothorax was tried but no free pleural space was found. Pneumoperitoneum was instituted a few days later. Within a period of six weeks, cough became negligible and expectoration scanty. A film taken on March 29, 1941 showed no evidence of cavitation. Sputum conversion took place. However, although pneumoperitoneum refills were continued at weekly intervals, about June 3, 1941 there was a return to previous symptomatology and sputum was again found to be positive for tubercle bacilli. The vomica previously seen became evident once more. It was then decided to do a phrenic neurectomy on the right side. Pneumoperitoneum refills were continued. An excellent rise of the diaphragm on the right side, to a much higher level than could be obtained from pneumoperitoneum alone, resulted. The cavity became obliterated at the end of two months' time. Pneumoperitoneum was continued until the end of 1941 and then abandoned. A film taken on February 11, 1943 showed a fibrotic lesion in the right apex and no evidence of cavitation. For the past year, this man has been gainfully employed as a public accountant. He has gained forty pounds in weight. It is of interest to note that, although pneumoperitoneum showed apparent ability to close a subclavicular cavity, this beneficial result was of short duration and, in spite of the continuance of pneumoperitoneum, the cavity reappeared and obliteration was obtained only when a phrenicectomy was added.

CONCLUSIONS

The indications for pneumoperitoneum in the treatment of pulmonary tuberculosis may be summarized as follows:

(*1*) As a trial measure to determine diaphragmatic mobility and freedom from interfering subdiaphragmatic adhesions prior to phrenic interruption.

(*2*) In patients in whom a breakdown and reactivation of the tuberculous process have occurred some time after an effective phrenic operation, it may be possible by means of pneumoperitoneum to prevent reopening of the cavity.

(*3*) Its greatest value lies in its ability to enhance the value of the diaphragmatic rise following phrenic interruption.

(*4*) To prepare the patient for radical surgery and to make the lesion quiescent in less time than could be accomplished by bed-rest alone.

(*5*) Pneumoperitoneum *per se* is a measure of limited value. As the sole therapeutic measure for the treatment of pulmonary tuberculosis, its results are neither positive nor its benefits lasting.

CONCLUSIONES

Cabe sumarizar las indicaciones del neumoperitoneo en el tratamiento de la tuberculosis pulmonar en la forma siguiente:

(*1*) Como medida experimental para determinar la mobilidad diafragmática y la ausencia de adherencias subdiafragmáticas antes de la frenicectomía.

(*2*) En los enfermos en que se han presentado desintegración y reactivación del proceso tuberculoso algún tiempo después de ejecutarse una operación eficaz en el frénico, tal vez sea posible impedir la reabertura de las cavernas por medio del neumoperitoneo.

(*3*) Su valor máximo estriba en su capacidad para acrecentar el valor de la elevación del diafragma después de la intervención en el frénico.

(*4*) A fin de preparar al enfermo para la cirugía radical y aquietar la lesión en menos tiempo que el que se necesitaría con el encamamiento solo.

(*5*) El neumoperitoneo constituye *per se* un procedimiento de valor limitado. Como única medida terapéutica en la tuberculosis pulmonar, el resultado no es positivo, ni el beneficio duradero.

REFERENCES

(1) Banyai, A. L.: Pneumoperitoneum: Review of 220 cases, M. Rec., December 31, 1938, *148*, 431.

(2) Stokes, J. B.: Pneumoperitoneum for pulmonary tuberculosis, Illinois M. J., 1938, *73*, 137.

(3) Joanides, M., and Schlack, O. C.: Use of phrenic neurectomy combined with artificial pneumoperitoneum in collapse of adherent tubercular lung, J. Thoracic Surg., 1936, *6*, 218.

(4) Ellison, R. T.: Personal communication.

(5) Hobby, A. W.: Pneumoperitoneum adjunct treatment of pulmonary tuberculosis, Dis. of Chest, 1938, *4*, 18.

(6) Trimble, H. G., Eaton, J. L., and Moore, G.: Pneumoperitoneum in the treatment of pulmonary tuberculosis. The local effects on peritoneum, Am. Rev. Tuberc., 1939, *39*, 528.

ASCORBIC ACID IN TUBERCULOUS NAVAJO INDIANS

M. PIJOAN[1] AND B. SEDLACEK[2]

With assistance by C. A. Elkin[3] and R. L. Warren[3]

It has been shown by previous studies (1) that, under certain pathological conditions other than scurvy, the tissues may utilize increased amounts of ascorbic acid. In respect to patients with tuberculosis, Heinemann (2), as well as others (3, 4), has demonstrated ascorbic acid requirements which are two to three times in excess of the normal demand. No satisfactory explanation has been offered for the increased metabolic utilization of this vitamin in specific diseases. It is not the purpose of this investigation to explain the nature of this process, but rather to ascertain the plasma ascorbic acid levels in tuberculous Indians on a presumably "adequate" nutritional intake and to determine whether a need exists for a supplementary intake of ascorbic acid. There already exist such studies on Indains without tuberculous lesions (5).

GENERAL CONSIDERATIONS

The ideal method of study of ascorbic acid metabolism is to determine the degree of tissue saturation (6) as measured by known ascorbic acid intakes with reference to blood levels and urinary output. This type of data would yield an accurate index of the previous ascorbic acid utilization as well as the needs of the tissues. However, in field work where an ethnic hiatus exists, the only practical method is one which involves the dietary intake and the levels of ascorbic acid in plasma. Previous studies by Bessey and White (7) indicate that such a procedure is essentially satisfactory. The method employed involves the statistical collection of plasma values and the amount of ascorbic acid required in the diet over a period of time. It is, in fact, the only method of inquiry adaptable to our study.

In regard to daily requirements, Widenbauer (8) has shown that a daily intake of 22 mg. of ascorbic acid was necessary to maintain a fixed plasma level; Hathaway and Meyer (9) reported 31 mg.; and Bessey and White (7) arrived at the conclusion that three ounces of fresh orange juice, plus the ascorbic acid contained in the usual diet, seemed an ideal intake. The independent studies of Hauck (6) and Ralli (10) agree to an intake of 1.6 to 1.7 mg. a day per kilogram of body weight in order to hold the tissues in a state of vitamin C saturation. Todhunter and Robbins (11) have further found that for a maintenance of a blood plasma level about 1 mg. of ascorbic acid, 60 mg. per normal adult was required. Sherman (12), on the other hand, states that from 25 to 50 mg. is sufficient for normal body economy.

[1] U. S. Indian Service Laboratory and the Department of Chemistry, University of New Mexico, Albuquerque, New Mexico.

[2] Executive Medical Director, Navajo Service, U. S. Indian Service.

[3] Fellows of the School of Inter American Affairs, University of New Mexico, Albuquerque, New Mexico.

There seems to be some conflict of ideas as to adequate ascorbic acid intake. The differences in opinion seem to center on just what plasma level is desirable or is to be considered the "normal" value in blood. If, for purposes of contrast, it should be argued that a blood sugar level of 180 mg. per cent (venous renal threshhold) is necessary for energy requirements, then the higher ascorbic acid intakes would appear to be physiologically sound. On the other hand, a great difficulty would be encountered in sustaining a constant venous blood sugar level of 180 mg. per cent, just as it is somewhat difficult to maintain a constant high ascorbic acid level with sustained ascorbic acid elimination by the kidney. Our feeling is that this analogy is justified. Blood levels of from 0.8 mg. to 1.0 mg. per 100 cc. plasma can be maintained by normal subjects on approximately 25 to 50 mg. a day. This would be in keeping with Sherman's view (12) and with the work of Bessey and White (7) as well as with our findings among medical students (13). In our experience, no clinical symptoms of avitaminosis C occur unless the plasma level falls below 0.3 mg. in the plasma. Such symptoms are varied and not consistent, manifestations of frank scurvy occurring below 0.1 mg. per cent. To summarize, the criterion used is from 0.8 to 1.0 mg. per cent or slightly more for a normal value of ascorbic acid in plasma, and levels below 0.8 mg. indicate an early continued shortage in the diet. In our opinion, values of less than 0.7 mg. per cent indicate levels sufficiently low to be compatible with inadequate ascorbic acid metabolism.

METHODS AND MATERIALS

The subjects used for this investigation were patients at the Fort Defiance Sanatorium: 66 Navajo Indians, confined to bed with moderately advanced pulmonary tuberculosis. A careful record of the dietary had been kept and this was used to calculate the ascorbic acid intake. The possible losses in oxidation of the ascorbic acid were taken into consideration.

Blood samples were drawn from veins (emanating from median basilic) and placed in chemically clean tubes containing isotonic oxalate. Centrifugalization and assay were done with the least possible delay. The method of assay used was that of Mindlin and Butler (14).

RESULTS

Graphically and for purposes of convenience, the results are expressed in table 1.

It can be seen from table 1 that a definite improvement in ascorbic acid levels occurred on a supplementary intake. The change in patients with low plasma ascorbic acid levels to a subsequent increase by a supplemental intake of ascorbic acid is less than in a subject who approaches saturation. By this we mean that an increase from 0.24 to 0.3 per cent in plasma, on [32] + [50] mg. of ascorbic acid intake a day, is less than the increase on the same dosage from an initial level of 0.84 mg. per cent to 1.0 mg. This interesting relationship has been suggested by saturation studies of other investigators. In short, we believe that it would take less ascorbic acid, irrespective of tuberculosis, to change a higher

plasma value (over 0.8 and less than 1.2 mg. per cent) than it would to change a lower plasma value. Plasma values of over 1.0 mg. indicate approximate saturation as a urinary excretion of some consequence takes place at about that level.

TABLE 1

Ascorbic acid mg. per cent in plasma

Initial values and after fifteen days supplemental ascorbic acid intake

All figures represent mg. ascorbic acid

CASE	DIETARY INTAKE = 32 SUPPLEMENTAL INTAKE = 0	DIETARY INTAKE = 32 SUPPLEMENTAL INTAKE = 50	CASE	DIETARY INTAKE = 32 SUPPLEMENTAL INTAKE = 100	DIETARY INTAKE = 32 SUPPLEMENTAL INTAKE = 100	CASE	DIETARY INTAKE = 32 SUPPLEMENTAL INTAKE = 0	DIETARY INTAKE = 32 SUPPLEMENTAL INTAKE = 150
	Initial plasma value	Plasma level		Initial plasma value	Plasma level		Initial plasma value	Plasma level
	mg. per cent	*mg. per cent*		*mg. per cent*	*mg. per cent*		*mg. per cent*	*mg. per cent*
M. B.	0.74	0.74	C. T.	0.50	0.65	A. B.	0.50	0.74
B. T. B.	0.60	0.65	L. W.	0.74	1.0	R. N.	0.60	0.87
M. U.	0.50	0.65	M. T.	0.60	0.74	D. B.	0.24	0.30
B. Y.	0.60	0.74	L. P.	0.60	0.87	A. T.	0.50	0.65
C. B.	0.74	0.87	S. J.	0.74	0.87	J. D.	0.60	0.87
M. K.	0.74	0.87	E. B.	0.39	0.44	A. C. B.	0.50	0.74
A. T.	0.50	0.65	D. T.	0.74	0.87	E. L.	0.60	1.0
A. M.	0.39	0.44	C. B.	0.74	0.87	R. L.	0.85	1.0
B. D.	0.50	0.65	M. M.	0.50	0.65	A. S.	0.74	0.87
G. Y.	0.60	0.65	M. N.	0.50	0.65	A. C.	0.39	0.44
B. J.	0.60	0.65	M. C.	0.60	0.74	A. N.	0.50	0.65
W. Y.	0.60	0.87	P. T.	0.30	0.44	G. C.	0.74	0.87
F. B.	0.50	0.65	C. B.	0.50	0.65	N. B.	0.74	0.87
R. B.	0.74	0.87	R. N.	0.74	0.87	D. B.	0.60	0.74
O. P.	0.50	0.65	J. B.	0.50	0.65	L. J.	0.74	0.87
F. W.	0.24	0.30	F. N.	0.85	1.0	P. S.	0.60	0.74
R. W.	0.50	0.65	L. L.	0.74	0.87	C. L.	0.39	0.44
J. N.	0.50	0.65	B. C.	0.74	0.87	E. L.	0.50	0.65
D. B.	0.50	0.65	F. J.	0.60	0.74	E. J.	0.50	0.65
J. T.	0.60	0.74	W. C.	0.60	0.74	C. Y.	0.24	0.30
L. B.	0.85	1.0	L. J.	0.50	0.74	T. C.	0.60	0.87
B. L.	0.50	0.65	N. B.	0.39	0.44	A. G.	0.85	1.0

In our studies, where 100 mg. of ascorbic acid a day was added to a dietary intake of 32 mg., the relationship of plasma change in regard to initial levels can be expressed as follows, where $dy = \tan \alpha dx = \left(\frac{dy}{dx}\right) dx$, and where $dy/dx = 0.4x$: thus—

$$dy = \frac{dy}{dx}\, dx = 0.4x\, dx$$

or

$$\int dy = \int 0.4\ (dx)$$

Because the foregoing equation expresses one or several metabolic changes, dependent on the degree of tissue saturation following a constant dosage, the figures in plasma content cannot be treated statistically to our satisfaction. Thus no standard deviation $\sqrt{\frac{\Sigma d^2}{n}}$ would give a true insight into the picture of changes. It can be said roughly that the resulting change in plasma (from the initial plasma level) in column I (32 + 50 mg.) is a 17.6 per cent improvement; in column II (32 + 150 mg.) it is 22.5 per cent. However, on the basis of equation (a), those with less ascorbic acid in their plasma require more, and it is suggested that those with values below 0.4 mg. a day receive 400 mg. daily for approximately six days (a total of 1,800 mg.) and be subsequently placed on $\frac{32 + 50}{1.1}$ (calculated from the mean basis of change of the higher plasma value changes) = 74 mg. a day (in the tuberculous subjects).

This would appear to be a fairly satisfactory intake (excluding the relationship of intake to body weight) in subjects with tuberculosis of moderate activity after initial saturation with ascorbic acid has taken place.

It is realized that, ideally, saturation studies in relationship to surface area would be a more satisfactory approach. However, field conditions and other circumstances prevented the use of such a method which is time consuming in itself and requires the full coöperation of the patient. Assuming that the intake of ascorbic acid required to maintain normal subjects is about 30 mg. a day, it would appear from our findings that the tuberculosis patient requires at least twice as much, possibly more, depending on the patient, the extensiveness of the disease, etc. This is in direct support of previous findings in the literature.

DISCUSSION

It would seem evident that the supplementary intake of ascorbic acid should be in synthetic preparations, since great losses of the vitamin (oxidation induced by catalysts) are incurred in food preparation and in the contact of citrus fruits and tomatoes with metal. It has been recommended, for instance, that rather than give patients orange juice prepared in the kitchen, they be given whole oranges which they may peel and ingest.

Since the principal treatment of tuberculosis is to increase all factors pertinent to body economy and the recuperative resiliency of the patient towards this disease, it would seem that, aside from maintaining adequate haemoglobin, weight gains, etc., it would be of value to sustain a plasma level of a vitamin intimately connected with collagen formation (15). Furthermore, this vitamin is used quickly by the tissues and is not stored appreciably, as are some of the other vitamins. This does not necessarily mean that vitamin C is to be specifically used in the treatment of tuberculosis as a therapeutic agent, but rather as an adjunct to maintain proper ascorbic metabolism compatible with effective body economy.

CONCLUSION

Low ascorbic acid levels were found in tuberculous patients on an average intake of 32 mg. per day. Improvement in the plasma level followed an increase

in the ascorbic acid intake and a larger than normal demand for this vitamin was found to exist in tuberculous patients. The subject of diet and supplemental intake of this organic acid is discussed.

CONCLUSIÓN

En los tuberculosos que consumían un promedio de 32 mg. diarios de ácido ascórbico, encontráronse tenores bajos de dicho ácido. El tenor en el plasma mejoró al aumentarse la ingestión del ácido, descubriéndose en los tuberculosos una demanda sobrenormal en cuanto a dicha vitamina. Discútese también aquí la alimentación y la ingestión complementaria del ácido órganico.

REFERENCES

(1) Warren, H. A., Pijoan, M., and Emery, E. S.: Ascorbic acid requirements in patients with peptic ulcer, New England J. Med., 1939, *220*, 1061.

(2) Heinemann, M.: Ascorbic acid requirements in human tuberculosis, Acta brev. Neerland, 1937, *7*, 48.

(3) Abbasy, M. A., Harris, L. J., and Ellman, P.: Excretion of vitamin C in pulmonary tuberculosis and rheumatoid arthritis, Lancet, 1937, *2*, 181.

(4) Hasselbach, F.: Vitamin C deficiency in tuberculosis, Expt. Sta. Rec., 1936, *78*, 138.

(5) Pijoan, M., Elkin, C. A., and Eslinger, C. O.: Ascorbic acid deficiency among Papago Indians, J. Nutrition, 1943, *25*, 491.

(6) Belser, E. B., Hauck, H. M., and Storvick, C. A.: A study of the ascorbic acid intake required to maintain tissue saturation in normal adults, Ibid., 1939, *17*, 513.

(7) Bessey, O. A., and White, R. L.: Ascorbic acid requirements of children, Ibid., 1942, *26*, 195.

(8) Widenbauer, F.: Der Vitamin C—Haushalt des Menschen unter verschiedenen Verhältnissen, Klin. Wchnschr., 1937, *16*, 600.

(9) Hathaway, M. L., and Meyer, F. L.: Studies on the vitamin C metabolism of four pre-school children, J. Nutrition, 1941, *21*, 503.

(10) Ralli, E. P., and Friedman, G. J.: Response to feeding of cevitamic acid in normal and deficient subjects as measured by vitamin C excretory tests, Ann. Int. Med., 1938, *11*, 1996; J. A. M. A., 1938, *111*, 282.

(11) Todhunter, E. N., and Robbins, R. C.: Observations on the amount of ascorbic acid required to maintain tissue saturation in normal adults, J. Nutrition, 1940, *19*, 263.

(12) Sherman, H. C.: Chemistry of Food and Nutrition, 1941, chapt. XVII.

(13) Pijoan, M., and Klemperer, F.: Determination of blood ascorbic acid, J. Clin. Investigation, 1937, *16*, 443.

(14) Mindlin, R. L., and Butler, A. M.: The determination of ascorbic acid in plasma, J. Biol. Chem., 1938, *122*, 673.

(15) Wolbach, S. B.: Fundamental pathology of vitamin C, J. Pediat., 1938, *12*, 414.

BOOKS

DWIGHT O'HARA: *Air-borne Infection. Some Observations on Its Decline. Pp. ix + 114, New York, The Commonwealth Fund, 1943, cloth, $1.50.*

By EMIL BOGEN

This timely and stimulating discussion of the decline of respiratory diseases between the two world wars is based upon Massachusetts experience but has much wider application. It is fairly and objectively written, with a wealth of allusions to the course of diseases in the past, and an optimistic viewpoint as to the future. The chief factors involved in the decline of these diseases are depicted, and Osler's parable of the seed and the soil expanded to include the weeder as well. A few may question the inclusion of smallpox and rheumatic fever among the air-borne diseases, and the good natured gibes at immunization against pertussis, measles and scarlet fever, the ominous insinuation that eradicating tuberculosis will destroy "herd immunity" to the disease, or the espousal of sulfonamide prophylaxis against rheumatic fever. The combination of raw materials of health with emphasis on the standards of living and the minimizing of the emotional constitution may provoke the psycho-somaticists but seems warranted in a discussion limited to air-borne infection. The heart of the entire work, however, is involved in the discussion of the "natural amelioration" of the air-borne diseases which the author so strongly emphasizes.

Although the author recognizes that conscious preventive and therapeutic measures have been largely responsible for the decline in smallpox, diphtheria and tuberculosis mortality, he asserts that the decline, even in these diseases, really began before vaccination, serum, toxin antitoxin or toxoid, and sanatorium treatment were instituted. Part, then, of the later decline is also attributed to this "natural amelioration of the air-borne diseases" which seems only partly explained by the operation of cross immunities, naturally acquired specific immunities, nutritional and other improvements in living standards and other tangible factors. The concomitant decline in mortality from pneumonia, measles, whooping cough, scarlet fever and rheumatic fever is cited as evidence that this decline is not dependent upon human efforts.

The apparent depreciation of conscious control measures against air-borne respiratory diseases should not receive unthinking acquiescence. The asserted declines in smallpox, diphtheria and tuberculosis before the institution of public health measures were, actually, rare, slight and transitory, as compared with those which have followed their application. In most places and at most times, these diseases faithfully reflect the efforts which have been exerted against them. The decline in smallpox came first and proceeded in different places as vaccination became established; diphtheria showed successive drops as increasingly effective measures became available; and tuberculosis death rates, which started to fall in England with the establishment of Brompton Hospital and other institutions for the indoor relief of consumptives, as shown by Newsholme, in the

middle of the last century, and in America following the discovery of the tubercle bacillus and the beginning of the sanatorium movement here, as described by Hoffman, were still rising at last report in Japan where sanatoria were scarce.

Decline in pneumonia mortality, as shown in O'Hara's curves, did not begin until after the first world war, and the decline during the following two decades may have reflected as much the lessened general use of alcohol and the improved general living conditions, as the specific and nonspecific therapeutic measures, though the widened use of oxygen and serum in pneumonia cannot be denied some credit. The sharp drop with the use of the sulfonamides, however, seems unmistakeable. The decline in the death rate from whooping cough, measles and scarlet fever reflected, to a great extent, the declining birth rate and consequent decline in the number of children in the age of greatest susceptibility until very recently, but also participates in the influences which affect pneumonia, since a large part of the deaths from these diseases result from secondary pneumonic involvement.

The general decline in air-borne infections has been less marked than that among milk and water-borne diseases which took place in the preceding generation, but has been conspicuous as compared with the noninfectious diseases, such as diabetes, gastric ulcer, hypertension, coronary thrombosis or cancer, which have shown no such decrease during this time. It is hard to see why a general "ameliorating" principle or guardian angel should be so restricted. Survival of the fit, improved general living standards, adaptation of man and disease, etc. might be expected to apply to the one group no less than to the other. Does it not seem more reasonable to suppose that it is the increased knowledge of the nature of air-borne transfer and the measures taken to cut down such infection, as well as increased means of establishing specific immunity, which should be credited with the change?

This controversy is not a purely academic hair-splitting exercise. The energy and persistence with which public health movements are carried on depend upon the belief in their value. If sunspots and inevitable chromosomal interactions are going to abolish tuberculosis, why bother with expensive and unplesant early diagnosis campaigns of horrifying publicity, why spend millions on institutionalization, why exhaust doctors and patients in arduous campaigns of collapse therapy. But if God helps those who help themselves, if the decline in air-borne infection is the direct result of what has been done by man to make it decline, and if our success in the future control of air-borne infections is to be measured in terms of what we are doing against them, we receive increased inspiration to intensify our efforts.

The March of Medicine. The New York Academy of Medicine Lectures to the Laity, 1942. Pp. xiv + 217, New York, Columbia University Press, 1943, cloth, $2.50.

By LEWIS J. MOORMAN

This interesting volume contains a foreword by Dr. Malcolm Goodridge, President of the New York Academy of Medicine, giving expression to timely recogni-

tion of the fact that the layman should be informed about the history, the art and the romance of medicine. Also, "the less technical management of disease." He lists the distinguished lecturers with their respective subjects and commends the book to both physicians and laymen.

In the concise introduction, Dr. Herbert B. Wilcox calls attention to the fact that "mental and physical health are not the gifts of the gods, but come rather as a result of the acquirement of information and its adaptation to individual needs." He states that these lectures are not altogether lay in expression and content, but are designed to interest and stimulate both the laity and the profession.

The six lectures contained in this volume are listed as follows: "Tuberculosis: The Known and The Unknown," The Linsly R. Williams Memorial Lecture, James Alexander Miller, M.D., Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University; "The Brain and The Mind," Tracy Jackson Putnam, M.D., Professor of Neurology and Neurosurgery, Columbia University; "The Freudian Epoch," A. A. Brill, Ph.B., M.D., Lecturer in Post-Graduate Course, Neurology and Psychiatry, College of Physicians and Surgeons, Columbia University; "Genius, Giftedness, and Growth," Arnold Gesell, M.D., Director of The Clinic of Child Development, The School of Medicine, Yale University; "The History of the B-Vitamins," Norman Jolliffe, M.D., Associate Professor of Medicine, New York University, College of Medicine; and "The Newer Knowledge of Nutrition," A. J. Carlson, M.D., Professor of Physiology (Emeritus), University of Chicago.

Careful attention to these intriguing subjects, with studious integration of the authoritative knowledge offered by the respective authors, should be most helpful to laymen and doctors alike.

In these stressful times with the added strain of war upon us, what could be more important than to study the growth and development of mind and body as influenced by environment from birth to maturity? What more stimulating than the possible growth of genius from our genes, rather than the theory of its rare descent from on high? Doctor Gesell's lecture on "Genius, Giftedness and Growth" leads to serious contemplation of many problems which are worthy of sustained thought.

Now that we have increasing food limitations through rationing and other influences on supply and demand, the chapters on "The History of the B-Vitamins" and "The Newer Knowledge of Nutrition" assume a value of mounting significance. Doctors Jolliffe and Carlson have made available many important facts. It is to be hoped that the perusal of these chapters may help the average layman to acquire a more logical and more economical vitamin I.Q. than that offered through the channels of printed advertising and the extravagant claims of the radio barker.

With the increasing knowledge of our innate nervous instability, the chapters on "The Brain and The Mind" and "The Freudian Epoch" are well worth a careful reading. In the former, Doctor Putnam courageously surveys a difficult subject and, after advancing both fact and theory concerning the structure and function of the brain, he stresses the incompleteness of our knowledge, admits the

presence of unbridged gaps and leaves us hanging in the puzzling realm between science and philosophy, with the consciousness of the need of continued, clear thinking on all available clinical and experimental phenomena.

Doctor Brill's remarks on the development of the Freudian system should be of great interest to physicians and to many curious laymen. The knowledge contained in this chapter may encourage some to seek help through psychoanalysis, but on the other hand, it may deter many. To those who prize individual psychological integrity, the thought of letting down all inhibitions and giving free expression to every spontaneous thought is distasteful.

"Tuberculosis, The Known and The Unknown" by James Alexander Miller, has been saved for the last; not that it is necessarily the best. But, always, when there is a war, there is an abiding union between tuberculosis and Mars. This is a wedding which requires the lucid wine of wisdom to win safety against disease and death. What the reader learns about adequate nutrition and the importance of mental poise in the chapters referred to above, will afford a better understanding of this comprehensive consideration of tuberculosis. Doctor Miller's detailed discussion on the known and the unknown leads to the conclusion that in spite of our advances, tuberculosis continues to be one of our most deadly foes and that, since we have failed to find a specific cure, our only hope rests upon intelligent and diligent coöperation between the medical profession and a well informed public. With the privations of war descending upon all nations, the knowledge contained in this volume should have world-wide dissemination.

Papers of a Pioneer—Sir Pendrill Varrier-Jones. Collected by Peter Fraser. Preface by the Rt. Hon. The Lord Horder; Introduction by Sir Humphry Davy Rolleston. Pp. 107, Hutchinson & Co. (Publishers), Ltd., London, New York, Melbourne, 1943, cloth.

By MAX PINNER

In this little book, Peter Fraser presents abstracts from the writings of Sir Pendrill Varrier-Jones, arranged in such a way that, disregarding the chronological order of the original papers (which are all contained in a bibliographical list), the material reads like a series of self-contained papers. Two facts are clearly demonstrated: first, that Sir Pendrill worked and lived for one purpose, the rehabilitation of the tuberculous patient; and second, that Sir Pendrill was a master of the pithy phrase, of the verbal clarion call.

The problem is succinctly stated: many tuberculous patients do not regain their full working capacity following medical or surgical treatment, many remain in a precarious balance between health and disease and experience repeated recurrences. *"Despite our encyclopaedic knowledge of the disease; despite all the admirable aids to treatment at our disposal, . . . we fail to rehabilitate our patients. We label them; we treat them; we discharge them. Physically, they derive benefit, often temporary. Financially, they encounter ruin, often permanent."*

The patient, discharged from a sanatorium as arrested, is confronted by this situation: *"No light job with adequate remuneration can be found . . . A light job means light wages . . . light wages mean an empty stomach . . ."* No public or

private help will solve the problem and preserve the courage and self-respect of the individual. *"It is far better to subsidise industry than idleness."* The logical solution is the industrial village settlement for the tuberculous, as exemplified by Papworth, "The Great Endeavour."

It is owing, in a large measure, to the pioneering efforts of Sir Pendrill Varrier-Jones, during a period of more than a quarter of a century, that schemes, such as Papworth, no longer need to be justified; they have proven their effectiveness, their necessity, their rationale and their feasibility. But such is the inertia and the complacency of—who is to blame?—that even England has but *one* Papworth and adequate rehabilitation schemes are still woefully few so that, as Sir Pendrill has pointed out so many times, much of the medical endeavor in tuberculosis is wasted in the vicious cycle of diagnosis, medical treatment, discharge to unfavorable working and living conditions, break-down, readmission.

The upsurging consciousness of social obligation may still bring to a fuller fruition Sir Pendrill's efforts and dream in the form of many more rehabilitation centres and, it may be hoped, in much more variegated projects.

This collection from Sir Pendrill's writings should find wide distribution, particularly among the persons holding the purse strings for community projects. Here are no appeals to charity, but to social responsibility, to rational public health planning and to good business sense.

Personnel Problems of Sanatoria Resulting from War Conditions. Report of a study made by the Committee on Sanatorium Standards, American Trudeau Society, Medical Section of the National Tuberculosis Association. Pp. 41, published by the National Tuberculosis Association, New York, 1943, paper.

By MAX PINNER

This subject is rapidly reaching the same conversational status as that of the weather according to Mark Twain. Yet, this report is evidence of a praiseworthy attempt "to do something about it." At least, to understand and measure the situation and to "view with alarm." This report shows in unimpassioned figures just how many fewer nurses, physicians and other employees were working in tuberculosis sanatoria last November (1942), as compared to November, 1941. In this case one might say that it is unfortunately inherent in figures, in statistical presentations, to be unimpassioned: they do not directly—not without translation—mirror the heartache and anxious efforts of superintendents, which appear here as percentage figures; they do not express the discomfort and anguish of patients who are not only deprived of some luxury service but of some essentials here and there and who, at the very best, must learn some new patience —waiting longer than previously to have a bell answered, for food, for medicine—for the bedpan. All such personal difficulties stand mute behind the figures. Nor do the figures indicate the ever-increasing turnover of personnel, its deterioration in experience, reliability, human fitness; nor the ever-increasing burden that the individual employee must assume beyond that expressible statistically in terms of hours of work.

At this writing, the data of this report are nearly ten months old. Undoubt-

edly, many a responsible worker in sanatoria sadly realizes now how good the conditions were in November, 1942. And the process continues and no end, no improvement is in sight.

The report shows how the situation (the enviable situation of November, 1942!) has been met. But all devices of getting along with less are limited in effect, are amelioration of symptoms and not treatment of the cause. One can hardly escape the impression that the seriousness of the situation is not sufficiently recognized by the authorities nor by the still existing reserve of volunteer aid.

This report is an important beginning. But it would seem that continued reports (stating up-to-the-minute conditions) should be made by both local and national agencies; reports should be implemented by appeals, if possible by constructive plans, if necessary by some form of official regulation.

ST. J. LEITNER: *Der Morbus Besnier-Boeck-Schaumann. Chronische epitheloidzellige Retikuloendotheliose sive Granulomatose. Pp. 138, with 37 illustrations, Benno Schwabe & Co., Basel, 1942, paper.*

By ELI H. RUBIN

In a detailed and scholarly presentation of the subject, Leitner describes the various manifestations of systemic sarcoidosis and reports 15 instances of his own. The latter are well documented with roentgenograms and tables. The syndromes under which the disease may appear are:

1: Eyes: (a) Uveoparotitis (Heerfordt's syndrome) and iridocyclitis
(b) Mikulicz disease

2: Skin: (a) Boeck's sarcoid or miliary lupoid
(b) Lupus pernio (Besnier)
(c) Sarcoid (Darier-Roussy)
(d) Angiolupoid (Brocq-Pautrier)

3: Bones: Ostitis multiplex cystoides (Jüngling)

4: Lymph nodes: Lymphogranulomatosis, benign (Schaumann)

5: Lungs: Torpid forms of disseminated tuberculosis (Schaumann, Assmann-Hantschmann) or small, nodular; large, nodular and flat forms of glandular-pulmonary localization (Leitner)

6: Other organs: (Liver, spleen, bone marrow, etc.) Universal, large-cellular, sclerosing hyperplasia (Mylius-Schürmann) or chronic, epithelioid cell reticuloendotheliosis or granulomatosis (Leitner)

The list of syndromes might have included noncaseating tuberculosis (Pinner), pseudo-tuberculosis (Snapper) and several others.

To the 17 instances of Boeck's disease which had been examined postmortem and reported by Pinner, in 1938, the author adds 14 additional references contain-

ing postmortem findings. Histologically, as is well known, the disease is characterized by the presence of the epithelioid tubercles composed of single or several giant cells, a peripheral layer of round cells and a rim of hyaline connective tissue. There is absent or very slight caseation.

The clinical manifestations of the disease and the various syndromes previously enumerated are described in detail and illustrated with case reports. It appears that originally the disease was considered a Scandinavian affliction because most of the reported cases were by Scandinavian authors. When it became apparent that the disease affected all the organs of the body, contributions on the subject appeared in practically all countries. The bibliography of fourteen pages is quite impressive.

Among the possible aetiological factors in the causation of the disease, tuberculosis seems to have much to support it, but the evidence is indirect and inconclusive. It has been noted that in warm, tropical countries, where tuberculosis of the skin is rare, Boeck's sarcoid is also a rarity. On the other hand, the disease is common in well tuberculized countries of the Northern Hemisphere. In Africa the disease is seldom observed; in North American Negroes the disease is frequent. Constitution seems to play a rôle since the disease has been observed in members of the same family. Although the disease has its greatest incidence in the ages between twenty and forty years, instances are on record of its occurrence in infants as young as three months, as well as in individuals past fifty years. The histological structure of the tubercle is, of course, significant evidence of its possible tuberculous origin. Tuberculosis in certain animals (rats, horses) assumes a sarcoid structure. But inasmuch as similar structures are encountered in leprosy, Leishmaniasis, Bang's disease, syphilis, typhus and rheumatism, the tuberculosis specificity is open to question, particularly since tubercle bacilli are seldom demonstrable in uncomplicated sarcoidosis.

In agreement with most authors, Leitner maintains that the prognosis of Boeck's sarcoid is good. This is confirmed by his 15 cases. Yet from the many instances in which death results from involvement of the brain and heart and from superimposed ulcerative tuberculosis, it would seem to the reviewer that the benignity of the disease has been somewhat overemphasized.

EDWARD W. HAYES: *Tuberculosis as It Comes and Goes. Pp. 187, with 42 illustrations, Monrovia, California, 1943, fabrikoid, $2.00.*

By FRED H. HEISE

This book contains 187 pages, 47 of which are used for diagrams of illustrative X-ray films. It has been written primarily for the patient to use as a text-book. With the fundamental knowledge so gained, he should be able to enter more closely into the partnership of himself and his physician to bring about his restoration to health and to prevent infection of others.

The various aspects of tuberculosis are treated briefly and as a rule in conformity with modern ideas. There is a short chapter on the history of the disease. The various types of tubercle bacilli are considered and the principal aspects of

infection are discussed. The difference between simple infection and clinical disease is described. Diagnosis, classification and treatment, prognosis and "curability" are discussed and explained. Diagrams are used to explain the classification and the mechanical or collapse forms of treatment. On the whole the book is well written and will prove useful in the education of the intelligent patient and others interested in tuberculosis. Some of the terminology perhaps could have been more fully and simply explained to be better understood by the average layman.

As with all texts on tuberculosis, some controversial issues arise. Thus, in the text, primary tuberculosis is intimately connected with lymphatic tuberculosis at the root of the lung and almost always is considered benign in character. In the experience of some, pulmonary tuberculosis, developing in young adults shortly after conversion of a negative to a positive skin test, frequently is not associated with detectable tracheobronchial or bronchopulmonary lymphatic enlargement, nor is the condition by any means overwhelmingly benign in character. Primary infection apparently reacts differently in the same kind of tissue at different ages.

One may question the statement that the major proportion of serious clinical tuberculosis develops among the individuals who received primary infection with tubercle bacilli during childhood. The experience of some, in studying the development of tuberculosis in nurses and medical students, would indicate that more serious disease develops in the previously negative skin reactors.

Whether or not the physician should show his patients their X-ray films seems to be a somewhat debatable question. Some with whom this question was discussed felt that the average patient did not possess sufficient fundamental knowledge to understand what was shown him and others felt that it led to confusion and depression. Some physicians would explain the disease fully and show the films only at the time of discharge from treatment.

One just criticism of the chapters on mechanical treatment is the failure to stress its limitations and to call attention to some of its frequent complications, especially those of pneumothorax.

There are other debatable questions. The book is well written and will prove itself of value to those who may seek the basic knowledge of tuberculosis.

Books Received

RAFAEL H. MARTÍNEZ: Biostatistical and Epidemiological Report on the Americas. Pp. 84, Pan American Sanitary Bureau, Washington, D. C., Pub. No. 195, February, 1943, paper.

ERICH URBACH: Allergy. With the collaboration of Philip M. Gottlieb. Pp. xxii + 1073, with 400 illustrations and 80 tables and charts, Grune & Stratton, New York, 1943, fabrikoid, $12.00.

Chronic Pulmonary Disease in South Wales Coalminers. II. Environmental Studies.

A.—Report by the Committee on Industrial Pulmonary Disease. B–G.—

Reports on Physical, Chemical and Petrological Studies by T. Bedford and C. G. Warner; H. V. A. Briscoe, P. F. Holt, N. Spoor and others; G. Nagelschmidt; A. Brammall and J. G. C. Leech; D. Hicks and G. Nagelschmidt; J. Ivon Graham and D. F. Runnicles; and co-workers. Pp. xi + 222, with many tables, charts and illustrations, London, His Majesty's Stationery Office, 1943, cardboard, 10s. 6d.

Conference on Tuberculosis Isolation. Sponsored by the California State Department of Public Health. Held at Los Angeles, March 20, 1943. Pp. iv + 86, with appendices of 12 pp., paper.

Notes on Gas Gangrene. Prevention: Diagnosis: Treatment. Medical Research Council War Memorandum No. 2, Revised Second Edition. Pp. 28, London, Published by His Majesty's Stationery Office, 1943, paper, 6d. (British Information Services, 30 Rockefeller Plaza, New York.)

Rehabilitation of the War Injured. A Symposium. Edited by William Brown Doherty and Dagobert D. Runes. Pp. 684, Philosophical Library, New York, 1943, cloth, $10.00.

AMERICAN TRUDEAU SOCIETY

Report of the California Trudeau Society Annual Meeting, 1943

The California Tuberculosis Association met in annual session on April 7 and 8, 1943 at Fresno, California. This was a joint meeting with the California Trudeau Society, which presented the Clinical Program. The program was streamlined to meet war needs. Many of the sessions were joint sessions of the Medical and Social Work Groups.

There were 120 physicians registered at the meeting.

The following officers were elected for the California Trudeau Society for the coming year:

Howard W. Bosworth, M.D., Los Angeles—President
Cabot Brown, M.D., San Francisco—President-Elect
Arthur Bruce Steele, M.D., Santa Barbara—Vice-President
David T. Proctor, M.D., Pasadena—Secretary-Treasurer

The following standing committees were appointed:

Post-Graduate and Under-Graduate Education

Edward Kupka, M.D., *Chairman*
Sidney J. Shipman, M.D.
Lloyd B. Dickey, M.D.

Program Committee

David T. Proctor, M.D., *Chairman*
Glenroy N. Pierce, M.D.
William Gordon Winter, M.D.

Nominating Committee

John C. Sharp, M.D., *Chairman*

Membership Committee

Arthur Bruce Steel, M.D., *Chairman*
James O. Greenwell, M.D.
J. Lloyd Eaton, M.D.

Following is a summary of the papers presented of particular medical interest:

Compulsory Hospitalization of Recalcitrant Tuberculous Patients by Edward J. Kupka, M.D., Chief, Bureau of Tuberculosis, California State Department of Public Health. He pointed out specifically that the Health Officer has the power to either quarantine or isolate infectious disease in California. This, of course, includes tuberculosis. Effective application of this depends upon coöperation of the courts and district attorney's offices. The public in some areas is not educated up to the point where this would be possible. However, in certain clear-cut cases where there is flagrant violation, this police power invested in the Health

Officer has been used to good effect. The plea is made for its extension where indicated.

John O. Rafferty, M.D., Coordinating Officer, State Department of Public Health, San Francisco, discussed this and pointed out that a new Health Officer in a rural county must go slow in putting into effect any such policy.

P. K. Telford, M.D., Chief, Division of Tuberculosis, Los Angeles County Health Department, Los Angeles, reported his favorable experiences with this procedure. It has been effectively used by him over a period of years.

Mr. A. L. Martin, of the Attorney General's Office of California, presented in some detail, the sections of the Health and Safety Code that applied, quoting cases in which there had been court decisions. He stressed the fact that this authority must be exercised prudently.

War Time Industrial Exposures in Relation to Tuberculosis by Clifford Kuh, M.D., Chief, Bureau of Industrial Hygiene, State Department of Public Health, San Francisco. He pointed out that the rôle of dust, fumes, gas and vapors, with the single exception of silica, has essentially negative effects on preëxisting tuberculosis. Asbestos may be an exception to this general statement. Arc welding, particularly has no deleterious effect. In summarizing his experiences in war industry in California, he showed that these were essentially in line with previous studies in this field. He stressed the fact that personal hygiene, rather than environmental hygiene, is the key to this situation.

War Time Tuberculosis Case Findings by Lt. Col. Esmond R. Long, M.C., U. S. Army. Colonel Long described the work in the Army Induction Centres, where they now also examine for the Navy, with 4 x 5 inch film. He was in the process of making an extensive personal inspection of most of the induction centres of the country. He has prepared a standard of interpretation of chest films for use in the local centres as a guide to rejection, deferment or acceptance in questionable cases. The Army standards differ from those of the Navy but are in agreement in essentials.

Comdr. Paul V. Greedy, M.D., U. S. N., presented case-finding from the standpoint of the Navy, describing their use of the 35 mm. film fluorograph, which appeared adequate to him.

Charles F. Blankenship, M.D., P. A. Surgeon, District Director, United States Public Health Service, San Francisco, described the favorable experience in applying these methods to the civilian population.

Mr. W. Ford Higby, Executive Secretary of the California Tuberculosis Association, told of the various places in California where these methods were being applied in case-finding especially in war industries, on what is beginning to be a large scale.

Mr. Neal C. Godfrey, Assistant Personnel Director, Basalt Rock Co., Napa, gave a detailed outline of the application of their fluoroscopic survey. It was interesting to note that 95 per cent of the men were examined on a purely voluntary basis. Details of the plan were explained to the employees, and sufficient ground work was laid, giving a definite understanding of the procedure to them. This,

together with the active coöperation of the industry itself, gave them a large response.

Robert S. Quinn, M.D., of Santa Rosa, discussed in a similar fashion the application of this type of work to a small sanatorium and County Health Department, showing that, while the figures might be different, the same general principles hold, and the cases found are in the same relation to the larger surveys.

Lung Flukes by Lt. Comdr. John Miller, M.D., U.S.N.R. He stated that this disease was contracted by Americans in the South Pacific as a result of eating pickled shell fish left by the fleeing Japanese. The lung fluke, or *Paragonomous Westermanni,* is endemic in the South Pacific Islands. It has a complicated life cycle, but human infection is mostly from crab or crayfish. Direct transfer of infection is possible. Differential diagnosis from other tropical diseases is necessary. There may be thoracic, abdominal or glandular symptoms. Brown flecks in a very tenacious sputum is suggestive. The eggs are found in fresh unstained sputum. X-ray examination of the chest may well be negative. Lung fluke infection should be suspected in any patient from the South Pacific who has chronic bronchial disease, a peculiar type of chest pain or thrombophlebitis. The diagnosis is essentially a laboratory procedure and depends upon finding the typical egg under the microscope.

Pulmonary Cystic Disease by Louis J. Ruschin, M.D., Senior Resident, Fairmont Hospital, San Leandro. This was discussed in considerable detail, with review of literature and a number of cases. Its relation to emphysema was clearly brought out. He concluded that a great variety of lung abnormalities and disorders have been lumped together under the same term "Cystic Lung." A number of cases reported on are of congenital origin, but recent observation seems to indicate that this number is much smaller than previously thought. Numerous persons born with apparently normal lungs develop pulmonary cystic cavernous structures later in life.

J. J. Singer, M.D., Associate Clinical Professor of Medicine, University of Southern California School of Medicine, Los Angeles, discussed this subject and was in general agreement, stating also that the treatment of acquired cysts of the lung is nonsurgical. They should be treated symptomatically by restricting activities and attention to the general health. In certain cases, surgery is indicated. He emphasized the use of iodized oil by direct puncture of the chest wall in diagnosis.

Tuberculosis among Student Nurses and Contact Examination in a General Hospital by John B. Barnwell, M.D., of the University of Michigan Hospital, Ann Arbor. He stated that studies showed that at Ann Arbor from July, 1932 to July, 1940 there was more tuberculosis among the entering student nurses than among the first year students in the College of Literature and Arts. This was true of the applicants before they entered their training in the hospital. No evidence was found that one month's training on a Tuberculosis Service was the only factor, or even the main factor, in producing infection and disease among student nurses. In some hospitals the cry has been raised: "Praise the Lord and X-ray all admissions!"

Chest Wounds in War by Emile F. Holman, M.D. of Stanford University. He stated that the wounds of entrance should be excised to uncover foreign material and prevent infection.

The Treatment of Symptomless Survey Tuberculosis was discussed by the following panel:

Sidney J. Shipman, M.D., San Francisco, Chairman
John B. Barnwell, M.D., Ann Arbor
Phillip H. Pierson, M.D., San Francisco
Howard W. Bosworth, M.D., Los Angeles
Carl R. Howson, M.D., Los Angeles

There was general agreement that the diagnosis is the important point. Before treating one of these cases as tuberculosis, a careful diagnostic study is obligatory to be sure, first, that it is tuberculosis and, second, to evaluate the stage of the disease present—whether or not positive sputum or stomach wash is present, and whether or not the lesion is progressive. Some patients discovered by X-ray surveys will need observation only; others will need simple institutional care; and others will need some type of active collapse therapy. This must be decided on the basis of the individual problem at hand and general rules are not applicable.

Motion Pictures of Surgical Procedures were presented *by Frank S. Dolley, M.D., of Los Angeles.* These have been developed for teaching purposes and cover most of the usual surgical procedures with reference to tuberculosis, as well as non-tuberculous diseases. This presentation evoked much interest and commendation.